

CALCIUM CHANNEL BLOCKERS

Background of the Invention

Field of the Invention

[0001] The present invention relates to certain dihydropyrimidine, dihydropyrimidone, dihydropyrimidinethione, and dihydropyridine compounds that can modulate the activity of calcium channels. These compounds can also be used for the treatment of diseases, such as cardiovascular disease, that are associated with calcium channels.

Description of the Related Art

[0002] The pharmacological function and importance of calcium antagonists or calcium channel blockers, has been well documented. See, for example, *R. A. Janis and D. J. Triggle "New developments in Ca²⁺ channel antagonists" Journal of Medicinal Chemistry, 26, 775-785 (1983)*. Among the calcium antagonists, 4-aryl-1,4-dihydropyridine-3,5-dicarboxylic diesters (DHPs) of the nifedipine type have become almost indispensable for the treatment of cardiovascular diseases. For a review on Structure Activity Relations (SAR) see, *S. Goldmann and J. Stoltefuss "1,4-Dihydropyridine: Effects of chirality and conformation on the calcium antagonist and calcium agonist activities" Angewandte Chemie International Edition (English) 30, 1559-1578 (1991)*. It was well documented that substitution on 4-phenyl ring is very crucial for pharmacological activity. Substituents at ortho or meta position improve the activity, whereas para substitution invariably decrease the activity. It was also published that bulkiness of ortho substituent, improves the calcium antagonist activity. *B. Loev, M. M. Goodman, K. M. Snader, R. Tedeschi, E. Macko, "Hantzsch-Type Dihydropyridine hypotensive Agents", Journal of Medicinal Chemistry 17, 956-965 (1974)*.

[0003] Voltage-gated calcium channels are large transmembrane proteins that regulate the intracellular concentration of calcium ions. They are classified into high (HVA) and low (LVA) voltage-activated channels according to the membrane potential at which they are activated. *E. Carbone and H. D. Lux . "A low voltage activated, fully inactivating Ca channel in vertebrate sensory neurons" Nature, 310, 501-502, (1984)*; *B. Nilius , P. Hess, J. B. Lansman and R. W. Tsien A novel type of cardiac calcium channel in ventricular cells. Nature, 316, 443-446. (1985)*; *M. C. Nowicky, A. P. Fox , R. W. Tsien. "Three types of neuronal calcium channels with different calcium agonist sensitivity" Nature 316, 440-443 (1985)*. LVA channels open and inactivate very fast, but deactivate about 10-100 times slower than HVA calcium channels. HVA channels require stronger membrane depolarizations to activate and can be divided further into N, P/Q, R and L-types based on their pharmacological properties. LVA channels can be detected in various tissues such as heart, brain, dorsal root ganglia and adrenal gland. The use of different search algorithms on mammalian expressed sequence tagged cDNAs or on similar sequences of the

nematode *Caenorhabditis elegans* led to the identification of several genes, three of which encoded LVA calcium channels (T-type channels) and they have been named as α_{1G} , α_{1H} , α_{1I} ; see Review, L. Lacinova, N. Klugbauer, F. Hofmann "Low voltage activated calcium channels: from genes to function" *Gen. Physiol. Biophys.*, 19, 121-136, (2000). Of the above stated types of calcium channels, L-type channels received wide attention. Among the L-type channel blockers, Dihydropyridines (DHP) is the most widely studied. But, most of the DHPs are not selective against T-type channels and DHPs inhibiting the T-type channels is still sparse.

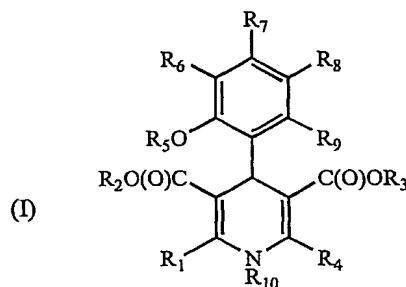
[0004] Voltage-gated calcium channels are important regulators of calcium influx in a number of cell types. Calcium entry through these channels activates a plethora of intracellular events, from the broad stimulation of gene expression, calcium-dependent second messenger cascades, and cell proliferation, to the specific release of neurotransmitter within the nervous system, and contraction in smooth and cardiac muscle (Tsien *et al.*, 1988)(Wheeler *et al.*, 1994); (Dunlap *et al.*, 1995); (Tsien *et al.*, 1991). A number of different types of calcium channels have been identified in native tissues and divided based on their biophysical profiles into low voltage activated (LVA) and high voltage activated (HVA) channels (Nowycky *et al.*, 1985); (Tsien *et al.*, 1991). LVA channels first activate at relatively hyperpolarized potentials and rapidly inactivate (Akaike *et al.*, 1989); (Takahashi *et al.*, 1991). By contrast, HVA channels require stronger membrane depolarizations to activate and can be divided further into N, P/Q-, R and L-types based on their pharmacological properties (for review, see (Stea *et al.*, 1995); (Zamponi, 1997)). Molecular cloning has revealed that HVA channels are heteromultimers comprised of a pore forming α_1 subunit plus ancillary α_2 - δ , β and possibly γ subunits (Pragnell *et al.*, 1994); (Klugbauer *et al.*, 1999); (Klugbauer *et al.*, 2000); for review, see (Catterall, 2000), whereas LVA channels appear to contain only the α_1 subunit (Lacinova *et al.*, 2000)). To date, ten different types of calcium channel α_1 subunits have been identified and shown to encode the previously identified native calcium channel isoforms. Expression studies show that alternative splicing of α_{1A} generates both P- and Q-type Ca^{2+} channels (Bourinet *et al.*, 1999), α_{1B} encodes N-type channels (Dubel *et al.*, 1992)) α_{1C} , α_{1D} and α_{1F} are L-type channels (Williams *et al.*, 1992b); (Bech-Hansen *et al.*, 1998), α_{1G} , α_{1H} and α_{1I} form T-type channels (i.e., McRory *et al.*, 2001) and α_{1E} may encode R-type channels (Soong *et al.*, 1993); (Tottene *et al.*, 1996), and α_{1S} encodes the skeletal muscle L-type channel isoform (Tanabe *et al.*, 1987).

[0005] Dihydropyridine (DHP) antagonists of L-type calcium channels are widely used therapeutics in the treatment of hypertension, angina, arrhythmias, congestive heart failure, cardiomyopathy, atherosclerosis, and cerebral and peripheral vascular disorders (Janis and Triggle, 1990) CRC Press, Cleveland. DHPs having a tendency to selectively block and enhance native L-type calcium channel activity. B. P.(Bean, 1984).; B. Z. (Peterson and Catterall, 1995). In addition

to L-type channel activity, some of the DHPs are sensitive to T-type channel activity. (N. Akaike, H. Kanaide, T. Kuga, M. Nakamura, J. Sadoshima and Tomoike "Low Voltage Activated Calcium Current in rat Aorta Smooth Muscle Cells In Primary Cultur" *J Physiol.* 416, 141-160, (1989).

Summary of the Invention

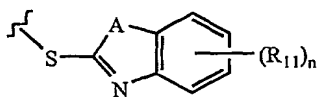
[0006] Disclosed are compounds of Formula I



or a pharmaceutically acceptable salt, amide, ester, or prodrug thereof,
where

- a) R_1 - R_8 are each independently selected from the group consisting of hydrogen, halogen, perhaloalkyl, nitro, amino, a diazo salt, optionally substituted lower alkyl, optionally substituted lower alkylene and optionally substituted five-membered or optionally substituted six-membered heteroaryl ring or optionally substituted six-membered aryl or heteroaryl ring,

where the lower alkyl and the lower alkylene moieties are each independently and optionally substituted with one or more substituents selected from the group consisting of halogen, perhaloalkyl, nitro, amino, hydroxy, alkoxy, sulfhydryl, thioether, cyano, amido, ester, and



where A is selected from the group consisting of oxygen, sulfur, and -NH and R_{11} is selected for the group consisting of hydrogen, hydroxy, alkoxy, haloalkoxy, halogen, haloalkyl, perhaloalkyl, nitro, amino, and a diazo salt, and n is between 0-4; and

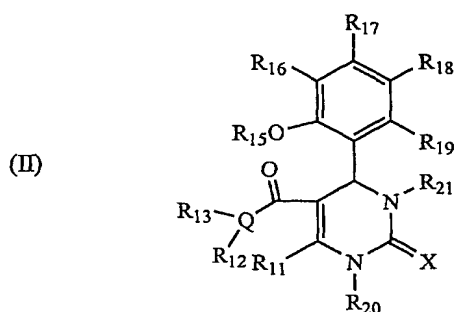
where the ring moieties are each independently and optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkylene,

- b) R_9 is selected from the group consisting of hydrogen, alkyl, alkylene, and a five-membered or six-membered heteroaryl ring or a six-membered aryl or heteroaryl ring, optionally substituted with one or more substituents selected from the group

consisting of lower alkyl, lower alkylene, halogen, perhaloalkyl, nitro, amino, cyano, amido, and ester; and

- c) R_{10} is selected from the group consisting of hydrogen and lower alkyl, or that R_{10} is optionally not present, in which case the nitrogen-containing ring in the compound of Formula I is an aromatic pyridine.

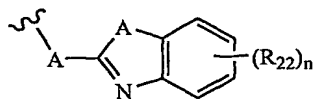
[0007] Furthermore, disclosed are compounds of Formula II



or a pharmaceutically acceptable salt, amide, ester, or prodrug thereof,
wherein

- a) R_{11} - R_{13} and R_{15} - R_{18} , are each independently selected from the group consisting of hydrogen, halogen, perhaloalkyl, nitro, amino, a diazo salt, optionally substituted lower alkyl, alkoxy, optionally substituted lower alkylene and optionally substituted five-membered or optionally substituted six-membered heteroaryl ring or optionally substituted six-membered aryl or heteroaryl ring, wherein

said lower alkyl and said lower alkylene moieties are each independently and optionally substituted with one or more substituents selected from the group consisting of halogen, perhaloalkyl, nitro, amino, hydroxy, alkoxy, sulfhydryl, thioether, cyano, amido, ester, and



A is selected from the group consisting of oxygen, sulfur, sulfoxide, sulfone, and -NH;

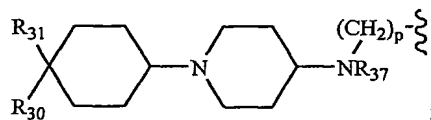
R_{22} is selected from the group consisting of hydrogen, hydroxy, alkoxy, haloalkoxy, halogen, haloalkyl, perhaloalkyl, nitro, amino, and a diazo salt; n is between 0-4; and

said ring moieties are each independently and optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkylene,

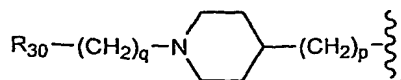
- b) R_{19} is selected from the group consisting of hydrogen, alkyl, alkylene, and a five-membered or six-membered heteroaryl ring or a six-membered aryl or heteroaryl ring, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkylene, halogen, perhaloalkyl, nitro, amino, cyano, amido, and ester; and
- c) R_{20} is selected from the group consisting of hydrogen and lower alkyl
- d) R_{21} is selected from the group consisting of:

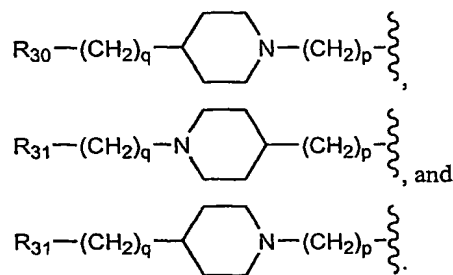
- i) hydrogen, alkyl, alkoxy, alkylene, and a five-membered or six-membered heteroaryl ring or a six-membered aryl or heteroaryl ring, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkylene, halogen, perhaloalkyl, nitro, amino, cyano, amido, and ester;
- ii) COY wherein Y is C_1 - C_8 alkyl, C_1 - C_8 alkoxy or $NR_{13}R_{14}$, wherein R_{13} is hydrogen or C_1 - C_8 alkyl and R_{14} is hydrogen, C_1 - C_8 alkyl, or C_1 - C_{14} phenalkyl;

- iii) X or COX wherein X is



- iv) halogen, CF_3 , cyano, nitro, $COONHR_{35}$, $COON(R_{35})_2$, $COOSO_2R_{38}$, $COONR_{35}SO_2N(R_{35})_2$, CO_2R_{35} , $COON(R_{35})_2$, $COOSO_2N(R_{35})_2$, $COOSO_2R_{38}$.
- v) $CONR_{25}R_{26}$, wherein R_{25} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, or arylalkyl and R_{26} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, or halosubstituted alkyl, or R_{25} and R_{26} taken together with the nitrogen atom to which they are attached form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 1-piperazinyl, 4-diarylalkyl-1-piperazinyl, each of which is optionally substituted with one or more substituents selected from the group consisting of alkyl, alkoxy, alkylthio, halo, trifluoromethyl, or hydroxy;
- vi) Z, COOZ, or $C(O)(NH)Z$, wherein Z is selected from the group consisting of





wherein

- A) p and q are each independently 0-10;
- B) R₃₀ is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, CF₃, cyano, nitro, N(R₃₅)₂, NR₃₅CONR₃₇, NR₃₅CON(R₃₇)₂, NR₃₅SO₂R₃₈, NR₃₅SO₂N(R₃₇)₂, (CH₂)₀₋₄CO₂R₃₅, (CH₂)₀₋₄CON(R₃₅)₂, (CH₂)₀₋₄SO₂N(R₃₅)₂, (CH₂)₀₋₄SO₂R₃₈, and C₁₋₄ alkyl;
- C) R₃₁ is selected from the group consisting of hydrogen, cyano, OR₃₈, COOR₃₅, CON(R₃₅)₂, and phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, CF₃, cyano, nitro, N(R₃₅)₂, NR₃₅CONR₃₇, NR₃₅CON(R₃₇)₂, NR₃₅SO₂R₃₈, NR₃₅SO₂N(R₃₇)₂, (CH₂)₀₋₄CO₂R₃₅, (CH₂)₀₋₄CON(R₃₅)₂, (CH₂)₀₋₄SO₂N(R₃₅)₂, (CH₂)₀₋₄SO₂R₃₈, and C₁₋₄ alkyl;
- D) R₃₅ and R₃₇ are each independently selected from hydrogen, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, (CH₂)₀₋₄CF₃; and
- E) R₃₈ is selected from the group consisting of hydrogen, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, and (CH₂)₀₋₄CF₃;

e) X is oxygen or sulfur; and

f) Q is oxygen or nitrogen; provided that when Q is oxygen R₁₃ does not exist.

[0008] Also disclosed is a method of modulating the activity of a calcium channel in a cell comprising the step of contacting the cell with a compound as described above.

[0009] In addition, disclosed is a method of treating a disease associated with a cellular calcium channel comprising identifying a subject in need of such treatment; and administering to the subject a therapeutically effective amount of a compound as described above.

[0010] Also disclosed is a method for inhibiting calcium T-channel activity, comprising the steps of providing a selective T-channel antagonist having an onset of activity in reducing systolic blood pressure in vivo of at least three hours and a duration of activity in vivo of at least 24 hours, where onset of activity refers to the time from administration to maximum

reduction of systolic blood pressure, and duration of activity refers to the time from administration until the maximum amount of systolic blood pressure reduction achieved subsequently decreases by at least 20 percent; and administering the antagonist to a mammal in regular doses no more often than once per day.

[0011] Furthermore, a method for treating hypertension is disclosed, which method comprises repeatedly administering to a patient a selective T-channel antagonist in individual dosages spaced at least one day apart.

[0012] In addition, disclosed is a method for selecting calcium T-channel antagonists having a desired pharmacological profile, comprising testing candidate compounds to measure rapidity of onset of activity; testing candidate compounds to measure duration of activity; and selecting candidate compounds having a slower onset of activity and a longer duration of activity than mibefradil.

[0013] Furthermore, pharmaceutical compositions are disclosed comprising a compound as described above, and a physiologically acceptable carrier, diluent, or excipient, or a combination thereof.

Brief Description of the Drawings

[0014] Figure 1 shows the single dose efficacy in spontaneously hypertensive rats, comparing PPK-5, Amlodipine, and Mibefradil.

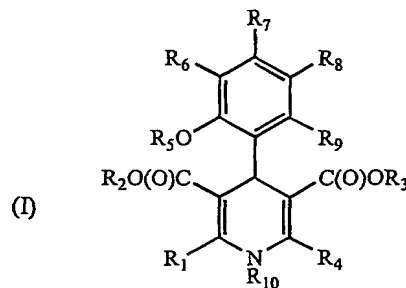
[0015] Figure 2 shows a multiple daily dose efficacy in spontaneously hypertensive rats, comparing PPK-5 and Mibefradil.

Detailed Description of the Preferred Embodiment

[0016] Here, we report a novel series of DHP derivatives (dialkyl-1,4-dihydro-4-(2'-alkoxy-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylates) derived from anacardic acid, a phenolic constituent present in cashew nut shell liquid (*Paul and Yeddanapalli, 1956*), (*1956*). These compounds exhibit activity as calcium channel antagonists, and can be used for the various purposes for which these types of compounds are known.

I. Compounds of the Invention

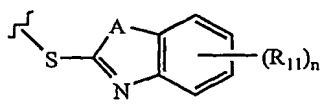
[0017] Thus, an aspect of the present invention relates to a compound of Formula I



or a pharmaceutically acceptable salt, amide, ester, or prodrug thereof,
where

- a) R_1 - R_8 are each independently selected from the group consisting of hydrogen, halogen, perhaloalkyl, nitro, amino, a diazo salt, optionally substituted lower alkyl, optionally substituted lower alkylene and optionally substituted five-membered or optionally substituted six-membered heteroaryl ring or optionally substituted six-membered aryl or heteroaryl ring,

where the lower alkyl and the lower alkylene moieties are each independently and optionally substituted with one or more substituents selected from the group consisting of halogen, perhaloalkyl, nitro, amino, hydroxy, alkoxy, sulfhydryl, thioether, cyano, amido, ester, and



where A is selected from the group consisting of oxygen, sulfur, and -NH and R_{11} is selected for the group consisting of hydrogen, hydroxy, alkoxy, haloalkoxy, halogen, haloalkyl, perhaloalkyl, nitro, amino, and a diazo salt, and n is between 0-4; and

where the ring moieties are each independently and optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkylene,

- b) R_9 is selected from the group consisting of hydrogen, alkyl, alkylene, and a five-membered or six-membered heteroaryl ring or a six-membered aryl or heteroaryl ring, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkylene, halogen, perhaloalkyl, nitro, amino, cyano, amido, and ester; and
- c) R_{10} is selected from the group consisting of hydrogen and lower alkyl, or that R_{10} is optionally not present, in which case the nitrogen-containing ring in the compound of Formula I is pyridine.

[0018] The term "pharmaceutically acceptable salt" refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. Pharmaceutical salts can be obtained by reacting a compound of the invention with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Pharmaceutical salts can also be obtained by reacting a compound of the invention with a base to form a salt such as an

ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like.

[0019] The term "ester" refers to a chemical moiety with formula $-(R)_n-COOR'$, where R and R' are independently selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), and where n is 0 or 1.

[0020] An "amide" is a chemical moiety with formula $-(R)_n-C(O)NHR'$ or $-(R)_n-NHC(O)R'$, where R and R' are independently selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), and where n is 0 or 1. An amide may be an amino acid or a peptide molecule attached to a molecule of the present invention, thereby forming a prodrug.

[0021] Any amine, hydroxy, or carboxyl side chain on the compounds of the present invention can be esterified or amidified. The procedures and specific groups to be used to achieve this end is known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley & Sons, New York, NY, 1999.

[0022] A "prodrug" refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. An example, without limitation, of a prodrug would be a compound of the present invention which is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A further example of a prodrug might be a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to reveal the active moiety.

[0023] The term "aromatic" refers to an aromatic group which has at least one ring having a conjugated pi electron system and includes both carbocyclic aryl (e.g., phenyl) and heterocyclic aryl groups (e.g., pyridine). The term includes monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups. The term "carbocyclic" refers to a compound which contains one or more covalently closed ring structures, and that the atoms forming the backbone of the ring are all carbon atoms. The term thus distinguishes carbocyclic from heterocyclic rings in which the ring backbone contains at least one atom which is different

from carbon. The term "heteroaromatic" refers to an aromatic group which contains at least one heterocyclic ring.

[0024] As used herein, the term "alkyl" refers to an aliphatic hydrocarbon group. The alkyl moiety may be a "saturated alkyl" group, which means that it does not contain any alkene or alkyne moieties. The alkyl moiety may also be an "unsaturated alkyl" moiety, which means that it contains at least one alkene or alkyne moiety. An "alkene" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon double bond, and an "alkyne" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon triple bond. The alkyl moiety, whether saturated or unsaturated, may be branched, straight chain, or cyclic.

[0025] The alkyl group may have 1 to 40 carbon atoms (whenever it appears herein, a numerical range such as "1 to 40" refers to each integer in the given range; *e.g.*, "1 to 40 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 40 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 20 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 5 carbon atoms. The alkyl group of the compounds of the invention may be designated as "C₁-C₄ alkyl" or similar designations. By way of example only, "C₁-C₄ alkyl" indicates that there are one to four carbon atoms in the alkyl chain, *i.e.*, the alkyl chain is selected from the group consisting of methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl.

[0026] The alkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is(are) one or more group(s) individually and independently selected from cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, trihalomethanesulfonyl, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, ethenyl, propenyl, butenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. Wherever a substituent is described as being "optionally substituted" that substituent may be substituted with one of the above substituents.

[0027] The substituent "R" appearing by itself and without a number designation refers to a substituent selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon).

[0028] An "O-carboxy" group refers to a RC(=O)O- group, where R is as defined herein.

[0029] A "C-carboxy" group refers to a $-C(=O)OR$ groups where R is as defined herein.

[0030] An "acetyl" group refers to a $-C(=O)CH_3$, group.

[0031] A "trihalomethanesulfonyl" group refers to a $X_3CS(=O)_2-$ group where X is a halogen.

[0032] A "cyano" group refers to a $-CN$ group.

[0033] An "isocyanato" group refers to a $-NCO$ group.

[0034] A "thiocyanato" group refers to a $-CNS$ group.

[0035] An "isothiocyanato" group refers to a $-NCS$ group.

[0036] A "sulfinyl" group refers to a $-S(=O)-R$ group, with R as defined herein.

[0037] A "S-sulfonamido" group refers to a $-S(=O)_2NR-$ group, with R as defined herein.

[0038] A "N-sulfonamido" group refers to a $RS(=O)_2NH-$ group with R as defined herein.

[0039] A "trihalomethanesulfonamido" group refers to a $X_3CS(=O)_2NR-$ group with X and R as defined herein.

[0040] An "O-carbamyl" group refers to a $-OC(=O)-NR-$ group-with R as defined herein.

[0041] An "N-carbamyl" group refers to a $ROC(=O)NH-$ group, with R as defined herein.

[0042] An "O-thiocarbamyl" group refers to a $-OC(=S)-NR-$ group with R as defined herein.

[0043] An "N-thiocarbamyl" group refers to an $ROC(=S)NH-$ group, with R as defined herein.

[0044] A "C-amido" group refers to a $-C(=O)-NR_2$ group with R as defined herein.

[0045] An "N-amido" group refers to a $RC(=O)NH-$ group, with R as defined herein.

[0046] The term "perhaloalkyl" refers to an alkyl group where all of the hydrogen atoms are replaced by halogen atoms.

[0047] Unless otherwise indicated, when a substituent is deemed to be "optionally substituted," it is meant that the substituent is a group that may be substituted with one or more group(s) individually and independently selected from cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, trihalomethanesulfonyl, and amino, including mono- and di-substituted amino groups, and the

protected derivatives thereof. The protecting groups that may form the protective derivatives of the above substituents are known to those of skill in the art and may be found in references such as Greene and Wuts, above.

[0048] In certain embodiments, in the compound of Formula I, wherein R_1 and R_4 may each independently be hydrogen or lower alkyl. In other embodiments, R_1 and R_4 may be lower alkyl. The lower alkyl may optionally and independently be selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, and pentyl. In some embodiments, R_1 and R_4 are methyl.

[0049] Certain embodiments of the invention relate to a compound of Formula I, where R_2 and R_3 may each independently be hydrogen or lower alkyl. In other embodiments, R_2 and R_3 may be lower alkyl. The lower alkyl may optionally and independently be selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, and pentyl. In certain embodiments R_2 may be methyl, while in other embodiments R_2 may be ethyl. In some embodiments R_3 may be isopropyl, while in other embodiments R_3 may be methyl, and in still other embodiments R_3 may be isopropyl.

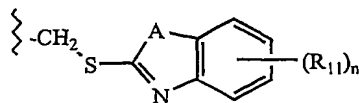
[0050] In some embodiments, R_5 of the compound of Formula I may be hydrogen or lower alkyl. In certain embodiments, R_5 may be lower alkyl. The lower alkyl may optionally and independently be selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, and pentyl. In certain embodiments R_5 may be methyl, while in other embodiments R_5 may be ethyl or isopropyl.

[0051] The R_6 - R_8 substituents of the compound of Formula I may in some embodiments each be independently hydrogen or lower alkyl. In certain embodiments, R_6 - R_8 are hydrogen.

[0052] Some embodiments relate to a compound of Formula I in which R_9 is hydrogen or alkyl. In certain embodiments, R_9 may be alkyl. In some embodiments R_9 may be a straight chain alkyl while in other embodiments R_9 may be a branched alkyl. R_9 may comprise at least 30, or 20, or 15, or 10, or 8, or 5, or at least 3 carbon atoms. In some embodiments R_9 is pentadecyl, which has the formula $-\text{CH}_2(\text{CH}_2)_{13}\text{CH}_3$.

[0053] The substituent R_{10} may be present or may be absent. In some embodiments R_{10} is present and is hydrogen. In other embodiments R_{10} is absent and the nitrogen containing ring in the compound of Formula I is an aromatic pyridine. Those of skill in the art understand that when R_{10} is present, to position 4 of the nitrogen-containing ring, i.e., the position to which the phenyl group is attached, an additional hydrogen, not shown in the above formula, is connected. Thus, there are four single bonds to the carbon of position four: two bonds within a ring, one bond to the phenyl group, and one bond to the hydrogen (not shown). However, when R_{10} is absent, no

hydrogen is attached to the carbon of position 4. The phenyl group would be the only group attached to that carbon, in addition to the bonds within the ring.



[0054] In certain embodiments, R_4 is $\text{---CH}_2\text{---S---}$, where A is selected from the group consisting of oxygen, sulfur, and -NH and R_{11} is selected from the group consisting of hydrogen, hydroxy, alkoxy, haloalkoxy, halogen, haloalkyl, perhaloalkyl, nitro, amino, and a diazo salt, and n is between 0-4.

[0055] A "diazo salt" is a group of formula $\text{---NN}^+\text{X}^-$, where X is a halogen. In some embodiments, the halogen is a chlorine, while in other embodiments, the halogen is a fluorine, or a bromine.

[0056] In some embodiments A is oxygen, while in other embodiments A is sulfur, and in still other embodiments A is -NH.

[0057] In certain embodiments, R_{11} is hydrogen.

[0058] In certain embodiments, the present invention relates to a compound of Formula I, where the compound is selected from the group consisting of

diethyl 1,4-dihydro-4-(2'-ethoxy-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate;

dimethyl 1,4-dihydro-4-(2'-ethoxy-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate;

diisopropyl 1,4-dihydro-4-(2'-ethoxy-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate;

diethyl 1,4-dihydro-4-(2'-methoxy-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate;

dimethyl 1,4-dihydro-4-(2'-methoxy-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate;

diisopropyl 1,4-dihydro-4-(2'-methoxy-6'-pentadecylphenyl)-2,6-dimethyl-3,5-carboxypyridine dicarboxylate;

diethyl 1,4-dihydro-4-(2'-isopropoxy-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate;

dimethyl 1,4-dihydro-4-(2'-isopropoxy-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate;

diisopropyl 1,4-dihydro-4-(2'-isopropoxy-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate;

diethyl 1,4-dihydro-4-(2'-methoxy-6'-pentadecylphenyl)-2-methyl-6-(2'-mercapto-1'H-benzimidazolyl)methyl-3,5-pyridine dicarboxylate;

dimethyl 1,4-dihydro-4-(2'-methoxy-6'-pentadecylphenyl)-2-methyl-6-(2'-mercapto-1'H-benzimidazolyl)methyl-3,5-pyridine dicarboxylate;

diisopropyl 1,4-dihydro-4-(2'-methoxy-6'-pentadecylphenyl)-2-methyl-6-(2'-mercapto-1'H-benzimidazolyl)methyl-3,5-pyridine dicarboxylate;

diethyl 1,4-dihydro-4-(2'-isopropoxy-6'-pentadecylphenyl)-2-methyl-6-(2'-mercapto-1'H-benzimidazolyl)methyl-3,5-pyridine dicarboxylate;

dimethyl 1,4-dihydro-4-(2'-isopropoxy-6'-pentadecylphenyl)-2-methyl-6-(2'-mercapto-1'H-benzimidazolyl)methyl-3,5-pyridine dicarboxylate;

diisopropyl 1,4-dihydro-4-(2'-isopropoxy-6'-pentadecylphenyl)-2-methyl-6-(2'-mercapto-1'H-benzimidazolyl)methyl-3,5-pyridine dicarboxylate;

diethyl 1,4-dihydro-4-(2'-ethoxy-6'-pentadecylphenyl)-2-methyl-6-(2'-mercapto-1'H-benzimidazolyl)methyl-3,5-pyridine dicarboxylate;

dimethyl 1,4-dihydro-4-(2'-ethoxy-6'-pentadecylphenyl)-2-methyl-6-(2'-mercapto-1'H-benzimidazolyl)methyl-3,5-pyridine dicarboxylate;

diisopropyl 1,4-dihydro-4-(2'-ethoxy-6'-pentadecylphenyl)-2-methyl-6-(2'-mercapto-1'H-benzimidazolyl)methyl-3,5-pyridine dicarboxylate;

1,4-dihydro-4-(2'-ethoxy-6'-pentadecylphenyl)-2,6-dimethyl-3-ethyl-5-(methoxyethyl)pyridine dicarboxylate;

1,4-dihydro-4-(2'-ethoxy-6'-pentadecylphenyl)-2,6-dimethyl-3-methyl-5-(methoxyethyl)pyridine dicarboxylate;

1,4-dihydro-4-(2'-ethoxy-6'-pentadecylphenyl)-2,6-dimethyl-3-isopropyl-5-(methoxyethyl)pyridine dicarboxylate;

1,4-dihydro-4-(2'-methoxy-6'-pentadecylphenyl)-2,6-dimethyl-3-ethyl-5-(methoxyethyl)pyridine dicarboxylate;

1,4-dihydro-4-(2'-isopropoxy-6'-pentadecylphenyl)-2,6-dimethyl-3-ethyl-5-(methoxyethyl)pyridine dicarboxylate;

diethyl 1,4-dihydro-4-(2'-ethoxy-6'-pentadecylphenyl)-2-(2'-aminoethoxy)methyl-6-methyl-3,5-pyridine dicarboxylate;

dimethyl 1,4-dihydro-4-(2'-ethoxy-6'-pentadecylphenyl)-2-(2'-aminoethoxy)methyl-6-methyl-3,5-pyridine dicarboxylate;

diisopropyl 1,4-dihydro-4-(2'-ethoxy-6'-pentadecylphenyl)-2-(2'-aminoethoxy)methyl-6-methyl-3,5-pyridine dicarboxylate;

diethyl 1,4-dihydro-4-(2'-methoxy-6'-pentadecylphenyl)-2-(2'-aminoethoxy)methyl-6-methyl-3,5-pyridine dicarboxylate;

dimethyl 1,4-dihydro-4-(2'-methoxy-6'-pentadecylphenyl)-2-(2'-aminoethoxy)methyl-6-methyl-3,5-pyridine dicarboxylate;

diisopropyl 1,4-dihydro-4-(2'-methoxy-6'-pentadecylphenyl)-2-(2'-aminoethoxy)methyl-6-methyl-3,5-pyridine dicarboxylate;

diethyl 1,4-dihydro-4-(2'-isopropoxy-6'-pentadecylphenyl)-2-((2'-aminoethoxy)methyl-6-methyl-3,5-pyridine dicarboxylate);

dimethyl 1,4-dihydro-4-(2'-isopropoxy-6'-pentadecylphenyl)-2-(2'-aminoethoxy)methyl-6-methyl-3,5-pyridine dicarboxylate;

diisopropyl 1,4-dihydro-4-(2'-isopropoxy-6'-pentadecylphenyl)-2-(2'-aminoethoxy)methyl-6-methyl-3,5-pyridine dicarboxylate;

diethyl 1,4-dihydro-4-(2'-ethoxy-3',5'-dinitro-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate;

dimethyl 1,4-dihydro-4-(2'-ethoxy-3',5'-dinitro-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate;

diisopropyl 1,4-dihydro-4-(2'-ethoxy-3',5'-dinitro-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate;

diethyl 1,4-dihydro-4-(2'-methoxy-3',5'-dinitro-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate;

dimethyl 1,4-dihydro-4-(2'-methoxy-3',5'-dinitro-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate;

diisopropyl 1,4-dihydro-4-(2'-methoxy-3',5'-dinitro-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate;

diethyl 1,4-dihydro-4-(2'-isopropoxy-3',5'-dinitro-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate;

dimethyl 1,4-dihydro-4-(2'-isopropoxy-3',5'-dinitro-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate;

diisopropyl 1,4-dihydro-4-(2'-isopropoxy-3',5'-dinitro-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate;

diethyl 1,4-dihydro-4-(2'-ethoxy-3',5'-diamino-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate;

dimethyl 1,4-dihydro-4-(2'-ethoxy-3',5'-diamino-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate;

diisopropyl 1,4-dihydro-4-(2'-ethoxy-3',5'-diamino-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate;

diethyl 1,4-dihydro-4-(2'-methoxy-3',5'-diamino-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate;

dimethyl 1,4-dihydro-4-(2'-methoxy-3',5'-diamino-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate;

diisopropyl 1,4-dihydro-4-(2'-methoxy-3',5'-diamino-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate;

diethyl 1,4-dihydro-4-(2'-isopropoxy-3',5'-diamino-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate;

dimethyl 1,4-dihydro-4-(2'-isopropoxy-3',5'-diamino-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate;

diisopropyl 1,4-dihydro-4-(2'-isopropoxy-3',5'-diamino-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate;

diethyl 1,4-dihydro-4-(2'-ethoxy-6'-pentadecylphenyl)-2-methyl-6-(5''-methyl-2-mercapto-1'H-benzimidazolyl)methyl-3,5-pyridine dicarboxylate;

dimethyl 1,4-dihydro-4-(2'-ethoxy-6'-pentadecylphenyl)-2-methyl-6-(5''-methyl-2-mercapto-1'H-benzimidazolyl)methyl-3,5-pyridine dicarboxylate;

diisopropyl 1,4-dihydro-4-(2'-ethoxy-6'-pentadecylphenyl)-2-methyl-6-(5''-methyl-2-mercapto-1'H-benzimidazolyl)methyl-3,5-pyridine dicarboxylate;

diethyl 1,4-dihydro-4-(2'-methoxy-6'-pentadecylphenyl)-2-methyl-6-(5''-methyl-2-mercapto-1'H-benzimidazolyl)methyl-3,5-pyridine dicarboxylate;

dimethyl 1,4-dihydro-4-(2'-methoxy-6'-pentadecylphenyl)-2-methyl-6-(5''-methyl-2-mercapto-1'H-benzimidazolyl)methyl-3,5-pyridine dicarboxylate;

diisopropyl 1,4-dihydro-4-(2'-methoxy-6'-pentadecylphenyl)-2-methyl-6-(5''-methyl-2-mercapto-1'H-benzimidazolyl)methyl-3,5-pyridine dicarboxylate;

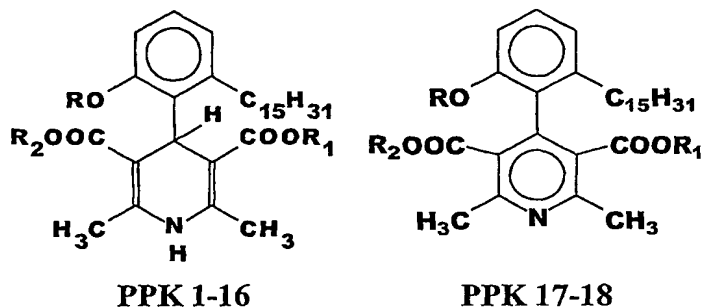
diethyl 1,4-dihydro-4-(2'-isopropoxy-6'-pentadecylphenyl)-2-methyl-6-(5''-methyl-2-mercapto-1'H-benzimidazolyl)methyl-3,5-pyridine dicarboxylate;

dimethyl 1,4-dihydro-4-(2'-isopropoxy-6'-pentadecylphenyl)-2-methyl-6-methyl(5'-methyl-2-mercapto-1'H-benzimidazolyl)methyl-3,5-pyridine dicarboxylate; and

diisopropyl 1,4-dihydro-4-(2'-isopropoxy-6'-pentadecylphenyl)-2-methyl-6-methyl(5'-methyl-2-mercapto-1'H-benzimidazolyl)methyl-3,5-pyridine dicarboxylate.

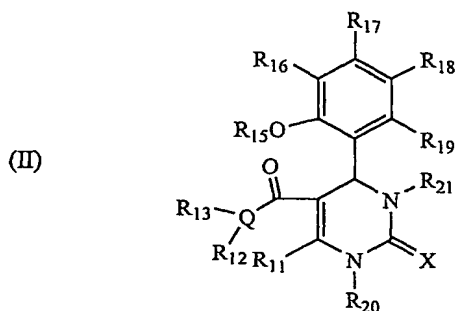
[0059] The structures of some of the above compounds are shown in Table 1.

Table 1



SAMPLE NAME	R	R ₁	R ₂
PPK-1	CH ₃	CH ₂ CH ₃	CH ₃
PPK-2	CH ₃	CH ₂ CH ₃	CH ₂ CH ₃
PPK-3	CH ₂ CH ₃	CH ₂ CH ₃	CH ₃
PPK-4	CH ₂ CH ₃	CH ₂ CH ₃	CH ₂ CH ₃
PPK-5	CH(CH ₃) ₂	CH ₃	CH ₃
PPK-6	CH(CH ₃) ₂	CH ₂ CH ₃	CH ₃
PPK-7	CH(CH ₃) ₂	CH ₂ CH ₃	CH ₂ CH ₃
PPK-8	CH ₃	CH(CH ₃) ₂	CH ₃
PPK-9	CH ₃	CH(CH ₃) ₂	CH ₂ CH ₃
PPK-10	CH ₃	CH(CH ₃) ₂	CH(CH ₃) ₂
PPK-11	CH ₂ CH ₃	CH(CH ₃) ₂	CH ₃
PPK-12	CH ₂ CH ₃	CH(CH ₃) ₂	CH ₂ CH ₃
PPK-13	CH ₂ CH ₃	CH(CH ₃) ₂	CH(CH ₃) ₂
PPK-14	CH(CH ₃) ₂	CH(CH ₃) ₂	CH ₃
PPK-15	CH(CH ₃) ₂	CH(CH ₃) ₂	CH ₂ CH ₃
PPK-16	CH(CH ₃) ₂	CH(CH ₃) ₂	CH(CH ₃) ₂
PPK-17	CH ₃	CH ₂ CH ₃	CH ₂ CH ₃
PPK-18	CH ₂ CH ₃	CH ₂ CH ₃	CH ₂ CH ₃

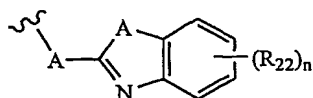
[0060] In another aspect, the present invention relates to a compound of Formula II



or a pharmaceutically acceptable salt, amide, ester, or prodrug thereof,
wherein

- a) R_{11} - R_{13} and R_{15} - R_{18} , are each independently selected from the group consisting of hydrogen, halogen, perhaloalkyl, nitro, amino, a diazo salt, optionally substituted lower alkyl, alkoxy, optionally substituted lower alkylene and optionally substituted five-membered or optionally substituted six-membered heteroaryl ring or optionally substituted six-membered aryl or heteroaryl ring, wherein

said lower alkyl and said lower alkylene moieties are each independently and optionally substituted with one or more substituents selected from the group consisting of halogen, perhaloalkyl, nitro, amino, hydroxy, alkoxy, sulfhydryl, thioether, cyano, amido, ester, and

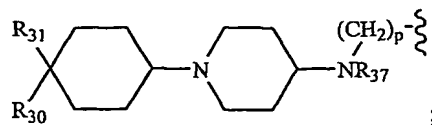


A is selected from the group consisting of oxygen, sulfur, sulfoxide, sulfone, and -NH;

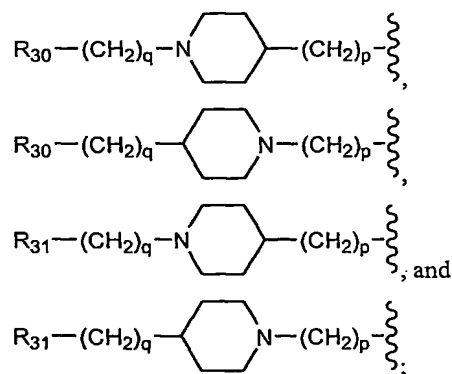
R_{22} is selected from the group consisting of hydrogen, hydroxy, alkoxy, haloalkoxy, halogen, haloalkyl, perhaloalkyl, nitro, amino, and a diazo salt; n is between 0-4; and

said ring moieties are each independently and optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkylene,

- b) R_{19} is selected from the group consisting of hydrogen, alkyl, alkylene, and a five-membered or six-membered heteroaryl ring or a six-membered aryl or heteroaryl ring, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkylene, halogen, perhaloalkyl, nitro, amino, cyano, amido, and ester; and
- c) R_{20} is selected from the group consisting of hydrogen and lower alkyl
- d) R_{21} is selected from the group consisting of:
- hydrogen, alkyl, alkoxy, alkylene, and a five-membered or six-membered heteroaryl ring or a six-membered aryl or heteroaryl ring, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower alkylene, halogen, perhaloalkyl, nitro, amino, cyano, amido, and ester;
 - COY wherein Y is C_1 - C_8 alkyl, C_1 - C_8 alkoxy or $NR_{13}R_{14}$, wherein R_{13} is hydrogen or C_1 - C_8 alkyl and R_{14} is hydrogen, C_1 - C_8 alkyl, or C_1 - C_{14} phenalkyl;
 - X or COX wherein X is



- iv) halogen, CF_3 , cyano, nitro, COONHR_{35} , $\text{COON}(\text{R}_{35})_2$, $\text{COOSO}_2\text{R}_{38}$, $\text{COONR}_{35}\text{SO}_2\text{N}(\text{R}_{35})_2$, CO_2R_{35} , $\text{COON}(\text{R}_{35})_2$, $\text{COOSO}_2\text{N}(\text{R}_{35})_2$, $\text{COOSO}_2\text{R}_{38}$.
- v) $\text{CONR}_{25}\text{R}_{26}$, wherein R_{25} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, or arylalkyl and R_{26} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, or halosubstituted alkyl, or R_{25} and R_{26} taken together with the nitrogen atom to which they are attached form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 1-piperazinyl, 4-diarylalkyl-1-piperazinyl, each of which is optionally substituted with one or more substituents selected from the group consisting of alkyl, alkoxy, alkylthio, halo, trifluoromethyl, or hydroxy;
- vi) Z , COOZ , or $\text{C}(\text{O})(\text{NH})\text{Z}$, wherein Z is selected from the group consisting of



wherein

- A) p and q are each independently 0-10;
- B) R_{30} is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, CF_3 , cyano, nitro, $\text{N}(\text{R}_{35})_2$, $\text{NR}_{35}\text{CONR}_{37}$, $\text{NR}_{35}\text{CON}(\text{R}_{37})_2$, $\text{NR}_{35}\text{SO}_2\text{R}_{38}$, $\text{NR}_{35}\text{SO}_2\text{N}(\text{R}_{37})_2$, $(\text{CH}_2)_{0-4}\text{CO}_2\text{R}_{35}$, $(\text{CH}_2)_{0-4}\text{CON}(\text{R}_{35})_2$, $(\text{CH}_2)_{0-4}\text{SO}_2\text{N}(\text{R}_{35})_2$, $(\text{CH}_2)_{0-4}\text{SO}_2\text{R}_{38}$, and C_{1-4} alkyl;
- C) R_{31} is selected from the group consisting of hydrogen, cyano, OR_{38} , COOR_{35} , $\text{CON}(\text{R}_{35})_2$, and phenyl optionally substituted with one or more substituents independently selected from the group

consisting of halogen, CF_3 , cyano, nitro, $\text{N}(\text{R}_{35})_2$, $\text{NR}_{35}\text{CONR}_{37}$, $\text{NR}_{35}\text{CON}(\text{R}_{37})_2$, $\text{NR}_{35}\text{SO}_2\text{R}_{38}$, $\text{NR}_{35}\text{SO}_2\text{N}(\text{R}_{37})_2$, $(\text{CH}_2)_{0-4}\text{CO}_2\text{R}_{35}$, $(\text{CH}_2)_{0-4}\text{CON}(\text{R}_{35})_2$, $(\text{CH}_2)_{0-4}\text{SO}_2\text{N}(\text{R}_{35})_2$, $(\text{CH}_2)_{0-4}\text{SO}_2\text{R}_{38}$, and C_{1-4} alkyl;

D) R_{35} and R_{37} are each independently selected from hydrogen, C_{1-8} alkyl, C_{3-8} cycloalkyl, $(\text{CH}_2)_{0-4}\text{CF}_3$; and

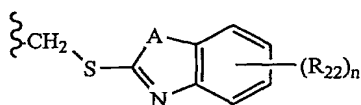
E) R_{38} is selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{3-8} cycloalkyl, and $(\text{CH}_2)_{0-4}\text{CF}_3$;

e) X is oxygen or sulfur; and

f) Q is oxygen or nitrogen; provided that when Q is oxygen R_{13} does not exist.

[0061] In certain embodiments, R_{11} is hydrogen or optionally substituted lower alkyl. In some of these embodiments, R_{11} is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, and pentyl. Some embodiments include those in which R_{11} is methyl or ethyl.

[0062] In other embodiments, R_{11} is



where A is selected from the group consisting of oxygen, sulfur, and $-\text{NH}$ and R_{22} is selected from the group consisting of hydrogen, hydroxy, alkoxy, haloalkoxy, halogen, haloalkyl, perhaloalkyl, nitro, amino, and a diazo salt, and n is between 0-4.

[0063] While in some embodiments A is oxygen, in other embodiments A is sulfur, and in still other embodiments A is $-\text{NH}$. In certain embodiments R_{22} is hydrogen.

[0064] In some embodiments, R_{12} and R_{13} are each independently hydrogen or lower alkyl. In some of these embodiments, R_{12} and R_{13} may each be independently selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, and pentyl.

[0065] In certain embodiments, R_{15} is hydrogen or lower alkyl. In some of these embodiments R_{15} may be selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, and pentyl.

[0066] Embodiments of the present invention include compounds of Formula II, in which R_{16} - R_{18} are each independently hydrogen or lower alkyl. In some embodiments R_{19} is hydrogen or alkyl. When R_{19} is alkyl, it may be a straight chain alkyl or a branched alkyl. In either case, R_{19} may comprise at least 30 carbon atoms, at least 20 carbon atoms, at least 15 carbon atoms, or at least 10 carbon atoms. Thus, R_{19} may be a pentadecyl ($\text{C}_{15}\text{H}_{31}$) group, a dodecyl ($\text{C}_{12}\text{H}_{25}$) group, or a decyl ($\text{C}_{10}\text{H}_{21}$) group.

[0067] In some embodiments, R_{20} is hydrogen.

[0068] In certain embodiments, R_{21} may be selected from the group consisting of hydrogen, alkyl, and alkoxy. When R_{21} is alkoxy, it may be selected from the group consisting of methoxy, ethoxy, and propoxy.

[0069] In some embodiments, R_{21} is COY, where Y is as defined herein. In certain of these embodiments Y is C_1 - C_8 alkoxy or $NR_{13}R_{14}$, where R_{23} is hydrogen or C_1 - C_8 alkyl and R_{24} is hydrogen, C_1 - C_8 alkyl, or C_1 - C_{14} phenalkyl. A "phenalkyl" group is one in which an optionally substituted phenyl group is attached to an alkyl substituent. Thus, $C_6H_5-CH_2-$ is a C_1 phenalkyl group. The phenyl group may be substituted as set forth herein.

[0070] In certain embodiments, Y may be a C_1 - C_4 alkoxy, which may be an ethoxy. In other embodiments Y may be $NR_{23}R_{24}$, where R_{23} and R_{24} may each be independently C_1 - C_8 alkyl. In some of these embodiments R_{23} and R_{24} are each methyl.

[0071] In some embodiments, R_{21} is selected from the group consisting of $COONHR_{35}$, $COON(R_{35})_2$, $COOSO_2R_{38}$, $COONR_{35}SO_2N(R_{35})_2$, CO_2R_{35} , $COON(R_{35})_2$, $COOSO_2N(R_{35})_2$, and $COOSO_2R_{38}$.

[0072] In other embodiments, R_{21} is X or COX, as X is defined herein, while in still other embodiments, R_{21} is Z, COOZ, or $C(O)(NH)Z$, as Z is defined herein. When R_{21} comprises the X substituent, p may be 0-8, 0-5, 0-3, or 0-2. In some embodiments p is 0, while in other embodiments p is 2. When R_{21} comprises the Z substituent, p and q may each independently be 0-8, 0-5, 0-3, or 0-2. In some embodiments p and q are each independently 0, while in other embodiments p and q are each independently 2.

[0073] Whether R_{21} comprises the X substituent or the Z substituent, R_{30} is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, CF_3 , cyano, nitro, $N(R_{35})_2$, $NR_{35}CONR_{37}$, $NR_{35}CON(R_{37})_2$, $NR_{35}SO_2R_{38}$, $NR_{35}SO_2N(R_{37})_2$, $(CH_2)_{0-4}CO_2R_{35}$, $(CH_2)_{0-4}CON(R_{35})_2$, $(CH_2)_{0-4}SO_2N(R_{35})_2$, $(CH_2)_{0-4}SO_2R_{38}$, and C_{1-4} alkyl. In some embodiments the phenyl is unsubstituted, while in other embodiments it is substituted. In certain of these embodiments, the phenyl is substituted with halogen, which may be a fluorine. In other embodiments the phenyl is substituted with $(CH_2)_{0-4}CO_2R_{35}$. In some of these latter embodiments, the phenyl may be substituted with $-COOCH_3$.

[0074] In certain embodiments Q is nitrogen. In some of these embodiments the moiety $-C(O)QR_{12}R_{13}$ may be $-C(O)NH_2$. In other embodiments Q is oxygen, in which case it is singly substituted and R_{13} does not exist.

[0075] Thus, some of the compounds of the above invention are listed in Table 2.

TABLE 2

Number	Name
PPK-21	5-ethoxycarbonyl-4-(2-ethoxy-6-pentadecylphenyl)-6-(2'-mercapto-1'H-benzimidazolyl) methyl-3,4-dihydropyrimidin-2(1H)-one
PPK-22	5-ethoxycarbonyl-4-(2-methoxy-6-pentadecylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one
PPK-23	5-methoxycarbonyl-4-(2-ethoxy-6-pentadecylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one
PPK-24	5-methoxycarbonyl-4-(2-methoxy-6-pentadecylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one
PPK-25	5-ethoxycarbonyl-4-(2-ethoxy-6-pentadecylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one
PPK-26A	5-methoxycarbonyl-4-(2-methoxy-6-(8' Z, 11' Z, 14' Z) pentadecatrienyl phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one
PPK-26B	5-methoxycarbonyl-4-(2-methoxy-6-(8' Z, 11' Z) pentadecadienyl phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one
PPK-26C	5-methoxycarbonyl-4-(2-methoxy-6-(8' Z) pentadecenyl phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one
PPK-27A	5-ethoxycarbonyl-4-(2-ethoxy-6-(8' Z, 11' Z, 14' Z) pentadecatrienyl phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one
PPK-27B	5-ethoxycarbonyl-4-(2-ethoxy-6-(8' Z, 11' Z) pentadecadienyl phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one
PPK-27C	5-ethoxycarbonyl-4-(2-ethoxy-6-(8' Z) pentadecenyl phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one
PPK-28A	5-methoxycarbonyl-4-(2-ethoxy-6-(8' Z, 11' Z, 14' Z) pentadecatrienyl phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one
PPK-28B	5-methoxycarbonyl-4-(2-ethoxy-6-(8' Z, 11' Z) pentadecadienyl phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one
PPK-28C	5-methoxycarbonyl-4-(2-ethoxy-6-(8' Z) pentadecenyl phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one
PPK-29A	5-isopropoxycarbonyl-4-(2-ethoxy-6-(8' Z, 11' Z, 14' Z) pentadecatrienyl phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one
PPK-29B	5-isopropoxycarbonyl-4-(2-ethoxy-6-(8' Z, 11' Z) pentadecadienyl phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one
PPK-29C	5-isopropoxycarbonyl-4-(2-ethoxy-6-(8' Z) pentadecenyl phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one
PPK-30	3,6-dihydro-4-methyl-6-[2-methoxy-6-pentadecylphenyl]-2-oxo-1,5-(2H)-pyrimidinedicarboxylic acid 1-ethyl 5-methyl diester
PPK-31	3,6-dihydro-4-methyl-6-[2-methoxy-6-pentadecylphenyl]-2-oxo-1,5-(2H)-pyrimidinedicarboxylic acid bis (ethyl ester)
PPK-32	3,6-dihydro-4-methyl-6-[2-methoxy-6-pentadecylphenyl]-2-oxo-1,5-(2H)-pyrimidinedicarboxylic acid 1-ethyl 5-isopropyl diester
PPK-33	3,6-dihydro-4-methyl-6-[2-ethoxy-6-pentadecylphenyl]-2-oxo-1,5-(2H)-pyrimidinedicarboxylic acid 1-ethyl 5-methyl diester
PPK-34	3,6-dihydro-4-methyl-6-[2-ethoxy-6-pentadecylphenyl]-2-oxo-1,5-(2H)-pyrimidinedicarboxylic acid 1,5-diethyl diester
PPK-35	3,6-dihydro-4-methyl-6-[2-ethoxy-6-pentadecylphenyl]-2-oxo-1,5-(2H)-pyrimidinedicarboxylic acid 1-ethyl 5-isopropyl diester
PPK-36	3,6-dihydro-4-methyl-6-[2-isopropoxy-6-pentadecylphenyl]-2-oxo-1,5-(2H)-pyrimidinedicarboxylic acid 1-ethyl 5-methyl diester
PPK-37	3,6-dihydro-4-methyl-6-[2-isopropoxy-6-pentadecylphenyl]-2-oxo-1,5-(2H)-pyrimidinedicarboxylic acid 1,5-diethyl diester
PPK-38	3,6-dihydro-4-methyl-6-[2-isopropoxy-6-pentadecylphenyl]-2-oxo-1,5-(2H)-pyrimidinedicarboxylic acid 1-ethyl, 5-isopropyl diester

Number	Name
PPK-41	3,6-dihydro-4-methyl-6-(2-methoxy-6-pentadecylphenyl)-2-thioxo-1,5(2H)-pyrimidine dicarboxylic acid bis (ethyl ester)
PPK-42	3,6-dihydro-4-methyl-6-(2-ethoxy-6-pentadecylphenyl)-2-thioxo-1,5(2H)-pyrimidine dicarboxylic acid bis (ethyl ester)
PPK-43	3,6-dihydro-4-methyl-6-(2-isopropoxy-6-pentadecylphenyl)-2-thioxo-1,5(2H)-pyrimidine dicarboxylic acid bis (ethyl ester)
PPK-44	3,6-dihydro-4-methyl-6-(2-methoxy-6-dodecylphenyl)-2-thioxo-1,5(2H)-pyrimidine dicarboxylic acid bis (ethyl ester)
PPK-45	3,6-dihydro-4-methyl-6-(2-ethoxy-6-dodecylphenyl)-2-thioxo-1,5(2H)-pyrimidine dicarboxylic acid bis (ethyl ester)
PPK-46	3,6-dihydro-4-methyl-6-(2-isopropoxy-6-dodecylphenyl)-2-thioxo-1,5(2H)-pyrimidine dicarboxylic acid bis (ethyl ester)
PPK-47	3,6-dihydro-4-methyl-2-thioxo-6-[2-isopropoxy-6-pentadecylphenyl]-1,5(2H)-pyrimidine dicarboxylic acid 5-ethyl-1-[1-(phenylmethyl)-4-piperidinyl]ester mono hydrochloride
PPK-48	3,6-dihydro-4-methyl-2-thioxo-6-[2-ethoxy-6-pentadecylphenyl]-1,5(2H)-pyrimidine dicarboxylic acid 5-ethyl-1-[1-(phenylmethyl)-4-piperidinyl]ester mono hydrochloride
PPK-49	1,2,3,4-tetrahydro-6-methyl-4-[2-methoxy-6-pentadecylphenyl]-3-(1-oxo-propyl)2-thioxo-5-pyrimidine carboxylic acid ethyl ester
PPK-50	1,2,3,4-tetrahydro-6-methyl-4-[2-ethoxy-6-pentadecylphenyl]-3-(1-oxo-propyl)2-thioxo-5-pyrimidine carboxylic acid ethyl ester
PPK-51	1,2,3,4-tetrahydro-6-methyl-4-[2-isopropoxy-6-pentadecylphenyl]-3-(1-oxo-propyl)2-thioxo-5-pyrimidine carboxylic acid ethyl ester
PPK-52	1-[(dimethyl amino)carbonyl]-1,2,3,6-tetrahydro-4-methyl-6-[2-methoxy-6-pentadecylphenyl]-2-thioxo-5-pyrimidine carboxylic acid ethyl ester
PPK-53	1-[(dimethyl amino)carbonyl]-1,2,3,6-tetrahydro-4-methyl-6-[2-ethoxy-6-pentadecylphenyl]-2-thioxo-5-pyrimidine carboxylic acid ethyl ester
PPK-54	1-[(dimethyl amino)carbonyl]-1,2,3,6-tetrahydro-4-methyl-6-[2-isopropoxy-6-pentadecylphenyl]-2-thioxo-5-pyrimidine carboxylic acid ethyl ester
PPK-55	3,6-dihydro-4-methyl-2-thioxo-6-[2-methoxy-6-pentadecylphenyl]-1,5(2H)-pyrimidinedicarboxylic acid, 5-ethyl-1-[1-(phenylmethyl)-4-piperidinyl] ester, monohydrochloride
PPK-56	3,6-dihydro-4-methyl-2-thioxo-6-[2-methoxy-6-pentadecylphenyl]-1,5(2H)-pyrimidinedicarboxylic acid, 5-(1-methylethyl) 1-[1-(phenylmethyl)-4-piperidinyl] ester, monohydrochloride
PPK-57	3,6-dihydro-4-methyl-2-thioxo-6-[2-ethoxy-6-pentadecylphenyl]-1,5(2H)-pyrimidinedicarboxylic acid, 5-(1-methylethyl) 1-[1-(phenylmethyl)-4-piperidinyl] ester, monohydrochloride
PPK-58	3,6-dihydro-4-methyl-2-thioxo-6-[2-ethoxy-3,5-dinitro-6-pentadecylphenyl]-1,5(2H)-pyrimidinedicarboxylic acid, 5-(1-methylethyl) 1-[1-(phenylmethyl)-4-piperidinyl] ester, monohydrochloride
PPK-59	1,2,3,6-Tetrahydro-4-methyl-1-[3-[methyl(phenylmethyl)amino]propyl]-2-thioxo-6-[2-methoxy-6-pentadecylphenyl]-5-pyrimidinecarboxylic acid, 1-methylethyl ester, monohydrochloride
PPK-60	1,2,3,6-Tetrahydro-4-methyl-1-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-2-thioxo-6-[2-methoxy-6-pentadecylphenyl]-5-pyrimidinecarboxylic acid, 1-methylethyl ester, monohydrochloride
PPK-61	3,6-dihydro-4-methyl-2-thioxo-6-[2-ethoxy-6-pentadecylphenyl]-1,5(2H)-pyrimidinedicarboxylic acid, 1-[1-[(4-florophenyl)methyl]-4-piperidinyl] 5-(1-methylethyl) ester, monohydrochloride
PPK-62	4-ethyl-5-methoxycarbonyl-1-{N-[3[4-(4-methoxycarbonyl)-4-phenylpiperidin-1-yl]propyl]carboxamido}-6-[2-methoxy-6-pentadecylphenyl]-2-oxo-1,2,3,6-tetrahydropyrimidine
PPK-63	4-ethyl-5-methoxycarbonyl-1-{N-[3[4-(4-methoxycarbonyl)-4-phenylpiperidin-1-yl]propyl]carboxamido}-6-[2-ethoxy-6-pentadecylphenyl]-2-oxo-1,2,3,6-tetrahydropyrimidine

Number	Name
PPK-64	5-carboxamido-4-ethyl-1-{N-[3-(4-methoxycarbonylphenyl)piperidin-1-yl]-propyl}carboxamido}-6-[2-methoxy-6-pentadecylphenyl]-2-oxo-1,2,3,6-tetrahydropyrimidine
PPK-65	4-ethyl-5-(N-methylcarboxamido)-1-{N-[3-(4-methoxycarbonylphenyl)piperidin-1-yl]propyl}carboxamido}-6-[2-methoxy-6-pentadecylphenyl]-2-oxo-1,2,3,6-tetrahydropyrimidine
PPK-66	5-methoxycarbonyl-1-{N-[3-[4-(4-methoxycarbonyl)-4-phenylpiperidin-1-yl]propyl]carboxamido}-4-methyl-6-[2-methoxy-6-pentadecylphenyl]-2-oxo-1,2,3,6-tetrahydropyrimidine
PPK-67	5-ethoxycarbonyl-1-{N-[3-[4-(4-methoxycarbonyl)-4-phenylpiperidin-1-yl]propyl]carboxamido}-4-methyl-6-[2-methoxy-6-pentadecylphenyl]-2-oxo-1,2,3,6-tetrahydropyrimidine
PPK-68	5-carboxamido-1-{N-[3-[4-(4-methoxycarbonyl)-4-phenylpiperidin-1-yl]propyl]carboxamido}-4-methyl-6-[2-methoxy-6-pentadecylphenyl]-2-oxo-1,2,3,6-tetrahydropyrimidine
PPK-69	1-{N-[3-[4-(4-methoxycarbonyl)-4-phenylpiperidin-1-yl]propyl]carboxamido}-4-methyl-5-(N-methylcarboxamido)-6-[2-methoxy-6-pentadecylphenyl]-2-oxo-1,2,3,6-tetrahydropyrimidine

[0076] The structures of the above compounds are shown in Table 3.

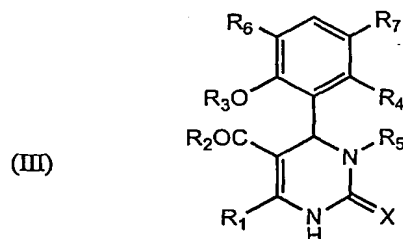
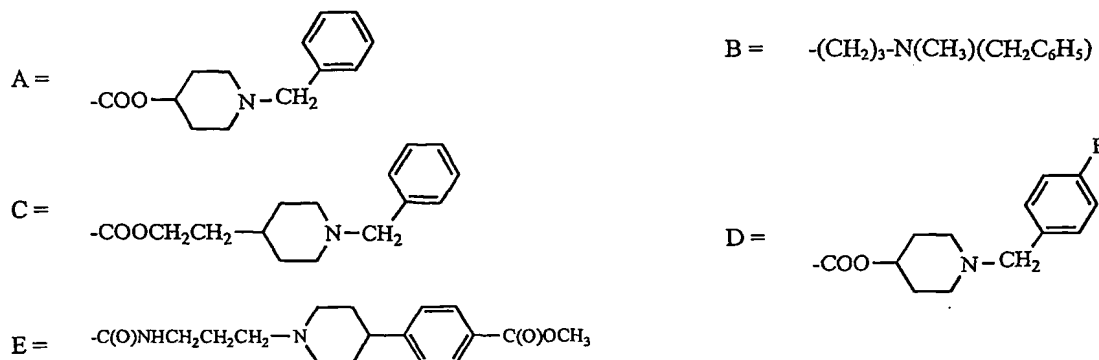


TABLE 3

Number	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	R ₇	X
PPK-21		ethoxy	ethyl	C ₁₅ H ₃₁	H	H	H	O
PPK-22	methyl	ethoxy	ethyl	C ₁₅ H ₃₁	H	H	H	O
PPK-23	methyl	methoxy	ethyl	C ₁₅ H ₃₁	H	H	H	O
PPK-24	methyl	methoxy	methyl	C ₁₅ H ₃₁	H	H	H	O
PPK-25	methyl	ethoxy	ethyl	C ₁₅ H ₃₁	H	H	H	O
PPK-26A	methyl	methoxy	methyl	(8'Z,11'Z,14'Z) pentadecatrienyl	H	H	H	O
PPK-26B	methyl	methoxy	methyl	(8'Z,11'Z) pentadecadienyl	H	H	H	O
PPK-26C	methyl	methoxy	methyl	(8'Z) pentadecenyl	H	H	H	O
PPK-27A	methyl	ethoxy	ethyl	(8'Z,11'Z,14'Z) pentadecatrienyl	H	H	H	O
PPK-27B	methyl	ethoxy	ethyl	(8'Z,11'Z) pentadecadienyl	H	H	H	O
PPK-27C	methyl	ethoxy	ethyl	(8'Z) pentadecenyl	H	H	H	O
PPK-28A	methyl	methoxy	ethyl	(8'Z,11'Z,14'Z) pentadecatrienyl	H	H	H	O
PPK-28B	methyl	methoxy	ethyl	(8'Z,11'Z) pentadecadienyl	H	H	H	O
PPK-28C	methyl	methoxy	ethyl	(8'Z) pentadecenyl	H	H	H	O

Number	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	R ₇	X
PPK-29A	methyl	isopropoxy	ethyl	(8'Z,11'Z,14'Z) pentadecatrienyl	H	H	H	O
PPK-29B	methyl	isopropoxy	ethyl	(8'Z,11'Z) pentadecadienyl	H	H	H	O
PPK-29C	methyl	isopropoxy	ethyl	(8'Z) pentadecenyl	H	H	H	O
PPK-30	methyl	methoxy	methyl	C ₁₅ H ₃₁	ethyl	H	H	O
PPK-31	methyl	ethoxy	methyl	C ₁₅ H ₃₁	ethyl	H	H	O
PPK-32	methyl	isopropoxy	methyl	C ₁₅ H ₃₁	ethyl	H	H	O
PPK-33	methyl	methoxy	ethyl	C ₁₅ H ₃₁	ethyl	H	H	O
PPK-34	methyl	ethoxy	ethyl	C ₁₅ H ₃₁	ethyl	H	H	O
PPK-35	methyl	isopropoxy	ethyl	C ₁₅ H ₃₁	ethyl	H	H	O
PPK-36	methyl	methoxy	isopropyl	C ₁₅ H ₃₁	ethyl	H	H	O
PPK-37	methyl	ethoxy	isopropyl	C ₁₅ H ₃₁	ethyl	H	H	O
PPK-38	methyl	isopropoxy	isopropyl	C ₁₅ H ₃₁	ethyl	H	H	O
PPK-41	methyl	ethoxy	methyl	C ₁₅ H ₃₁	COOEt	H	H	S
PPK-42	methyl	ethoxy	ethyl	C ₁₅ H ₃₁	COOEt	H	H	S
PPK-43	methyl	ethoxy	isopropyl	C ₁₅ H ₃₁	COOEt	H	H	S
PPK-44	methyl	ethoxy	methyl	C ₁₂ H ₂₅	COOEt	H	H	S
PPK-45	methyl	ethoxy	ethyl	C ₁₂ H ₂₅	COOEt	H	H	S
PPK-46	methyl	ethoxy	isopropyl	C ₁₂ H ₂₅	COOEt	H	H	S
PPK-47	methyl	ethoxy	isopropyl	C ₁₅ H ₃₁	A*	H	H	S
PPK-48	methyl	ethoxy	ethyl	C ₁₅ H ₃₁	A*	H	H	S
PPK-49	methyl	ethoxy	methyl	C ₁₅ H ₃₁	- OC ₃ H ₇	H	H	S
PPK-50	methyl	ethoxy	ethyl	C ₁₅ H ₃₁	- OC ₃ H ₇	H	H	S
PPK-51	methyl	ethoxy	isopropyl	C ₁₅ H ₃₁	- OC ₃ H ₇	H	H	S
PPK-52	methyl	ethoxy	methyl	C ₁₅ H ₃₁	CONM e ₂	H	H	S
PPK-53	methyl	ethoxy	ethyl	C ₁₅ H ₃₁	CONM e ₂	H	H	S
PPK-54	methyl	ethoxy	isopropyl	C ₁₅ H ₃₁	CONM e ₂	H	H	S
PPK-55	methyl	ethoxy	methyl	C ₁₅ H ₃₁	A	H	H	S
PPK-56	methyl	isopropoxy	methyl	C ₁₅ H ₃₁	A	H	H	S
PPK-57	methyl	isopropoxy	ethyl	C ₁₅ H ₃₁	A	H	H	S
PPK-58	methyl	isopropoxy	ethyl	C ₁₅ H ₃₁	A	-NO ₂	- NO ₂	S
PPK-59	methyl	isopropoxy	methyl	C ₁₅ H ₃₁	B	H	H	S
PPK-60	methyl	isopropoxy	methyl	C ₁₅ H ₃₁	C	H	H	S
PPK-61	methyl	isopropoxy	ethyl	C ₁₅ H ₃₁	D	H	H	S
PPK-62	ethyl	methoxy	methyl	C ₁₅ H ₃₁	E	H	H	O
PPK-63	ethyl	methoxy	ethyl	C ₁₅ H ₃₁	E	H	H	O
PPK-64	ethyl	-NH ₂	methyl	C ₁₅ H ₃₁	E	H	H	O
PPK-65	ethyl	-NH(CH ₃)	methyl	C ₁₅ H ₃₁	E	H	H	O
PPK-66	methyl	methoxy	methyl	C ₁₅ H ₃₁	E	H	H	O
PPK-67	methyl	ethoxy	methyl	C ₁₅ H ₃₁	E	H	H	O
PPK-68	methyl	-NH ₂	methyl	C ₁₅ H ₃₁	E	H	H	O
PPK-69	methyl	-NH(CH ₃)	methyl	C ₁₅ H ₃₁	E	H	H	O



II. Combination Therapy

[0077] While each compound of the present invention may be administered as the sole active ingredient in a pharmaceutical composition, the compounds of the present invention may be combined with other active ingredients in order to cause a more pronounced affect in the individual patient. Thus, in another aspect, the present invention relates to a pharmaceutical combination comprising a compound of Formula I or II, as described above, and a second compound.

[0078] In certain embodiments, the second compound may be an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB). A number of ACE inhibitors are commercially available. These compounds, whose chemical structure is somewhat similar, include lisinopril, enalapril, quinapril, ramipril, benazepril, captopril, fosinopril, moexipril, trandolapril, and perindopril. ACE inhibitors, generally, are compounds that inhibit the action of angiotensin converting enzyme, which converts angiotensin I to angiotensin II. The scope of the present invention includes all those ACE inhibitors now known and all those ACE inhibitors to be discovered in the future.

[0079] A number of ARBs are also commercially available or known in the art. These compounds include losartan, irbesartan, candesartan, telmisartan, eprosartan, and valsartan. ARBs reduce blood pressure by relaxing blood vessels. This allows better blood flow. ARBs function stems from their ability to block the binding of angiotensin II, which would normally cause vessels to constrict. The scope of the present invention includes all those ARBs now known and all those ARBs to be discovered in the future.

[0080] In other embodiments, the second compound in the pharmaceutical compositions of the present invention may be a beta-blocker. A number of beta-blockers are commercially available. These compounds include atenolol, metoprolol succinate, metoprolol tartrate, propranolol hydrochloride, nadolol, atenolol, acebutolol hydrochloride, bisoprolol fumarate, nadolol, pindolol, bisoprolol fumarate, acebutolol hydrochloride, betaxolol hydrochloride, penbutolol sulfate, timolol maleate, carteolol hydrochloride, esmolol hydrochloride,

and atenolol. Beta-blockers, generally, are β_1 and/or β_2 adrenergic receptor blocking agents, which decrease the positive chronotropic, positive inotropic, bronchodilator, and vasodilator responses caused by beta-adrenergic receptor agonists. The scope of the present invention includes all those beta-blockers now known and all those beta-blockers to be discovered in the future.

[0081] In another embodiment, the second compound is a cardiac (or digitalis) glycoside, such as digoxin.

[0082] In another aspect, the present invention relates to a pharmaceutical composition comprising a calcium channel blocker and a second compound. The calcium channel blocker may be selected from the group consisting of amlodipine, bepridil, diltiazem, isradipine, felodipine, mibefradil, nicardipine, nifedipine, nimodipine, nisoldipine, and verapamil. The second compound may be an ACE inhibitor, an ARB, or a beta-blocker, as described herein.

III. Methods of Treatment

[0083] In another aspect, the invention relates to a method of modulating the activity of a calcium channel in a cell comprising the step of contacting said cell with a compound of Formula I or II, as described above. The calcium channel being modulated may be a low voltage activated calcium channel or a high voltage activated calcium channel.

[0084] In a further aspect, the invention relates to a method of treating a disease associated with a cellular calcium channel comprising identifying a subject in need of such treatment, and administering to the subject a therapeutically effective amount of a compound of Formula I or II, as described above. In certain embodiments, the subject may be a mammal. The mammal may be selected from the group consisting of mice, rats, rabbits, guinea pigs, dogs, cats, sheep, goats, cows, primates, such as monkeys, chimpanzees, and apes, and humans. In some embodiments, the subject is a human.

[0085] Embodiments of the invention include those in which the disease to be treated is a cardiovascular disease. Examples of cardiovascular disease include arteriosclerosis, atherosclerosis, hypertension, unstable angina, cardiac arrhythmia, myocardial infarction, atrial fibrillation, and stroke.

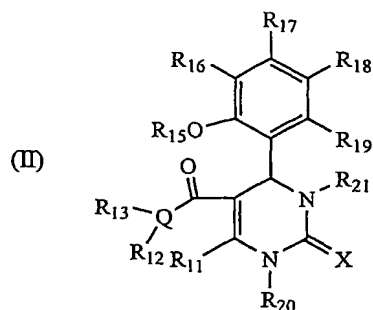
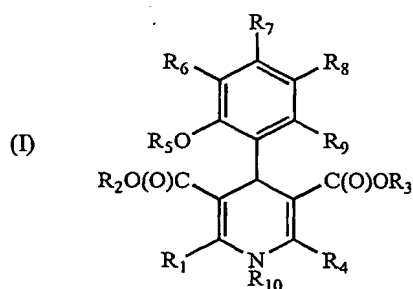
[0086] In other embodiments of the invention, the disease to be treated is migraine headaches, Raynaud's phenomenon (a condition in which arteries in the extremities spasm, causing pallor), menstrual cramps, spinal-cord injuries, kidney failure, cancer, or premature labor.

[0087] In another aspect, the invention relates to a method for inhibiting calcium T-channel activity, comprising the steps of providing a selective T-channel antagonist having an onset of activity in reducing systolic blood pressure *in vivo* of at least three hours and a duration of activity *in vivo* of at least 24 hours, wherein onset of activity refers to the time from administration to maximum reduction of systolic blood pressure, and duration of activity refers to the time from administration until the maximum amount of systolic blood pressure reduction achieved

subsequently decreases by at least 20 percent, and administering the antagonist to a mammal in regular doses no more often than once per day.

[0088] The term "onset of activity" refers to the time from the point of administration of the T-channel antagonist to the point where maximum reduction of systolic blood pressure is achieved. Following the period of onset of activity, the systolic blood pressure begins to rise, until eventually, the final systolic pressure reaches the same level as it was prior to the administration of the antagonist. Thus, over time the amount of systolic blood pressure reduction decreases, from the maximum reduction, to 90% of the maximum reduction, to 80% of the maximum reduction, etc., until to 20% of the maximum reduction, and then 10% of the maximum reduction. "Duration of activity" refers to the time from administration until the amount of maximum systolic blood pressure reduction achieved subsequently decreases by at least 20 percent.

[0089] In certain embodiments, the T-channel antagonist has a cyclic ring structure with a pendent alkylene group of at least 6 carbon atoms. In other embodiments, the T-channel antagonist is a compound of Formula I or II, described in Section I above:



where R_1 - R_{21} are as defined herein.

[0090] In certain embodiment, the T-channel antagonist is a prodrug.

[0091] In another aspect, the invention relates to a method for treating hypertension, comprising repeatedly administering to a patient a selective T-channel antagonist in individual dosages spaced at least one day apart.

[0092] In a further aspect, the invention relates to a method for selecting calcium T-channel antagonists having a desired pharmacological profile, comprising testing candidate compounds to measure rapidity of onset of activity; testing candidate compounds to measure duration of activity; and selecting candidate compounds having a slower onset of activity and a longer duration of activity than Mibefradil.

[0093] In some embodiments, at least one of the testing steps is performed in vitro; whereas in other embodiments at least one of the testing steps is performed in vivo.

[0094] Thus, any compound that is a selective T-channel antagonist, having a slower onset of activity and a longer duration of activity than Mibefradil is within the contemplation and

scope of the claims of the present invention. The onset of activity and the duration of activity can be measured by the assays described herein. Thus, in one aspect, the present invention relates to identifying a compound as a T-channel antagonist, determining its onset of activity and duration of activity by the methods described herein, compare those results with data known for Mibefradil, and determining that the compound has a slower onset of activity and a longer duration of activity than Mibefradil.

[0095] Several compounds have been tested in connection with the present invention. These tests demonstrate the relatively slow time course of block that can be accomplished with judicious selection of the administered compound.

[0096] Specifically, individual HEK cells were tested *in vitro* using a patch-clamp assay for T-channel blockage. Tests were performed at concentrations of 500 nM and 1 μ M, and the time course of the blockage was followed for a period of several minutes.

[0097] In the past, patch clamp assays for T-channel activity would measure inhibition of calcium-ion-mediated current over the course of only a few minutes, e.g., 2, 3, or 5 minutes. We have discovered that there are a number of active T-channel blockers that exhibit a surprisingly slow onset of activity, and a long time course of activity. The assays described herein can be used to differentiate between conventional-type T-channel blockers, which usually show a time constant of blockage of a few seconds, and the long-acting T-channel blockers, which show time constants between 1 minute and 2, 4, 5, 10 or more minutes. It is the latter group of compounds that is particularly interesting and useful in the present invention.

[0098] One conventional T-channel blocker, Mibefradil, exhibits a time constant of blockage of about 12 seconds. This time constant is described as one-third of the time required to achieve a complete blockage of current. In contrast, compounds of the present invention demonstrated a much slower time course of blockage. Preliminary numbers, which are subject to refinement with further studies, show the following:

<u>Compound</u>	<u>Time constant</u>
PPK5	8 minutes
PPK12	minutes
PPK22	1 minute
PPK21	minutes
PPK29	4.4 minutes
PPK35	10 minutes
PPK50	10 minutes
PPK51	13 minutes

[0099] Thus, each of the compounds exhibits a time constant of at least one minute, indicating extremely slow onset as compared to Mibefradil, with a time constant of 12 seconds.

However, in each case, the ED₅₀ (defined as the dosage required to achieve a 50% blockage of T-channel current) was between about 25 nM and about 1000 nM.

[0100] In addition to the referenced *in vitro* studies, *in vivo* studies have also been conducted. The *in vivo* hypertension model used here involves administration of compound to spontaneously hypertensive rats through IV tail injection of compound. Systolic blood pressure is then measured using a tail cuff.

[0101] In this study, as shown in Figure 1, PPK5 was administered in both a single dose study and a multiple dose study. The results of the single dose study (20mg/Kg) showed that systolic pressure dropped by about 48 mmHg in the first 5 hours, and dropped by about 55 mmHg in the first 10 hours, after which it remained at that level past 24 hours. In comparison, the known commercial T-channel blocker Mibefradil demonstrates a more volatile profile. When Mibefradil is administered (30mg/Kg oral), systolic blood pressure spikes down by about 85 mmHg in the first 5 hours, and then recovers slowly for the next 5 hours and then more rapidly, so that by the end of 24 hours, systolic blood pressure has recovered by about 45 mmHg. (Based on data from NDA for Mibefradil.)

[0102] Figure 2 references a multiple dose study in the spontaneously hypertensive rat. This study utilizes three injections of PPK5, spaced about 25 hours apart. A relatively slow onset is seen, with blood pressure dropping by about 55 mmHg, then remaining stable until the second injection, after which it drops by about an additional 12 mmHg, where it remains through the third injection until the end of the study. In contrast, 30 mg/Kg oral Mibefradil results in a rapid drop of 85 mmHg, followed by more than 50% recovery within 24 hours of administration. This demonstrates that a stable reduction of systolic pressure can readily be achieved using a compound of the present invention with a single daily dose, but that a conventional T-channel blocker that shows a much more rapid onset in *in vitro* studies is unsuitable for administration only once a day.

IV. Pharmaceutical Compositions

[0103] In another aspect, the invention relates to a pharmaceutical composition comprising a compound of Formula I or II, as described above, and a physiologically acceptable carrier, diluent, or excipient, or a combination thereof.

[0104] The term "pharmaceutical composition" refers to a mixture of a compound of the invention with other chemical components, such as diluents or carriers. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to, oral, injection, aerosol, parenteral, and topical administration. Pharmaceutical compositions can also be obtained by reacting compounds with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric

acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

[0105] The term "carrier" defines a chemical compound that facilitates the incorporation of a compound into cells or tissues. For example dimethyl sulfoxide (DMSO) is a commonly utilized carrier as it facilitates the uptake of many organic compounds into the cells or tissues of an organism.

[0106] The term "diluent" defines chemical compounds diluted in water that will dissolve the compound of interest as well as stabilize the biologically active form of the compound. Salts dissolved in buffered solutions are utilized as diluents in the art. One commonly used buffered solution is phosphate buffered saline because it mimics the salt conditions of human blood. Since buffer salts can control the pH of a solution at low concentrations, a buffered diluent rarely modifies the biological activity of a compound.

[0107] The term "physiologically acceptable" defines a carrier or diluent that does not abrogate the biological activity and properties of the compound.

[0108] The compounds described herein can be administered to a human patient *per se*, or in pharmaceutical compositions where they are mixed with other active ingredients, as in combination therapy, or suitable carriers or excipient(s). Techniques for formulation and administration of the compounds of the instant application may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, 18th edition, 1990.

a) Routes Of Administration

[0109] Suitable routes of administration may, for example, include oral, rectal, transmucosal, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intranasal, or intraocular injections.

[0110] Alternately, one may administer the compound in a local rather than systemic manner, for example, via injection of the compound directly into a solid tumor, often in a depot or sustained release formulation. Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with tumor-specific antibody. The liposomes will be targeted to and taken up selectively by the tumor.

b) Composition/Formulation

[0111] The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tableting processes.

[0112] Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more physiologically acceptable

carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in Remington's Pharmaceutical Sciences, above.

[0113] For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[0114] For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by mixing one or more solid excipient with one or more compound of the invention, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[0115] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0116] Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

[0117] For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

[0118] For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0119] The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

[0120] Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0121] Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

[0122] The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

[0123] In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0124] A pharmaceutical carrier for the hydrophobic compounds of the invention is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The cosolvent system may be the VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80™, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD:D5W) consists of VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of POLYSORBATE 80™; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, *e.g.*, polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

[0125] Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

[0126] Many of the compounds of the invention may be provided as salts with pharmaceutically compatible counterions. Pharmaceutically compatible salts may be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, *etc.* Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free acid or base forms.

c) Effective Dosage.

[0127] Pharmaceutical compositions suitable for use in the present invention include compositions where the active ingredients are contained in an amount effective to achieve its intended purpose. More specifically, a therapeutically effective amount means an amount of compound effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0128] For any compound used in the methods of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the IC_{50} as determined in cell culture. Such information can be used to more accurately determine useful doses in humans.

[0129] Toxicity and therapeutic efficacy of the compounds described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD_{50} and ED_{50} . Compounds which exhibit high therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See *e.g.*, Fingl *et al.* 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p. 1). Typically, the dose range of the composition administered to the patient can be from about 0.5 to 1000 mg/kg of the patient's body weight. The dosage may be a single one or a series of two or more given in the course of one or more days, as is needed by the patient.

[0130] The daily dosage regimen for an adult human patient may be, for example, an oral dose of between 0.1 mg and 500 mg, preferably between 1 mg and 250 mg, *e.g.* 5 to 200 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.01 mg and 100 mg, preferably between 0.1 mg and 60 mg, *e.g.* 1 to 40 mg of the compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Alternatively the compounds of the invention may be administered by continuous intravenous infusion, preferably at a dose of up to 400 mg per day. Thus, the total daily dosage by oral administration will be in the range 1 to 2000 mg and the total daily dosage by parenteral administration will be in the range 0.1 to 400 mg. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

[0131] Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from *in vitro* data; *e.g.*, the concentration necessary to achieve 50-90% of calcium channel blockage, using the assays known in the art. Dosages necessary to achieve the MEC will depend on

individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

[0132] Dosage intervals can also be determined using MEC value. Compounds should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%.

[0133] In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

[0134] The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

d) Packaging

[0135] The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, may be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

V. Synthesis of the Compounds of Formula I

[0136] The compounds of the general Formula I were prepared by the well-known Hantzsch dihydropyridine synthesis. In this method appropriate aldehyde was condensed with an appropriate beta keto esters like methyl acetoacetate, ethyl acetoacetate, isopropyl acetoacetate, ethyl 4-chloro acetoacetate and like, in inert solvent such as methanol, ethanol, isopropyl alcohol, n-butanol, an ether solvent such as 1,2-dimethoxyethane or tetrahydrofuran (THF), an amide solvent such as dimethyl formamide (DMF) or N-methylpyrrolidone, a sulfoxide solvent such as dimethyl sulfoxide (DMSO) or sulfolane, an aromatic hydrocarbon solvent such as benzene, toluene or xylene in presence of piperidine and acetic acid. If required, the knoevenegal product was purified by column chromatography and reacted with appropriate amino crotonate like methyl-3-amino crotonate, ethyl 3-amino crotonate, isopropyl 3-amino crotonate. The reaction is usually conducted at temperature from room temperature to 200 °C, preferably from 60 to 140 °C, for from 1-100 hours, preferably from 6 to 40 hours. The corresponding Hantzsch product was purified by column chromatography using silicagel (100-200 mesh) and/or crystallised using appropriate

organic solvents like hexane, petroleum ether (40-60 °C), ethanol etc. Substrates like 2-mercapto benzimidazole, (5 -methyl)2-mercapto benzimidazole, 2-amino ethanol and like as mentioned in claim 1 were used for substitutions on dihydropyridine ring.

[0137] For the processes mentioned above, any desired ratio of the substances participating in the reaction can be used. In general, however, the process is carried out with molar amounts of the reactants.

[0138] The synthesis of compounds includes enantiomerically pure forms obtained by methods such as, by separating diastereomer mixtures of the compounds of the general Formula I, from an enantiomerically pure chiral alcohol, by a customary method, subsequently preparing the enantiomerically pure carboxylic acids and/or any methods used for separation of enantiomers, for example, methods discussed by S. Goldmann and J. Stoltefuss [*S. Goldmann and J. Stoltefuss "1,4-Dihydropyridine: Effects of chirality and conformation on the calcium antagonist and calcium agonist activities" Angewandte Chemie International Edition (English) 30, 1559-1578 (1991)*].

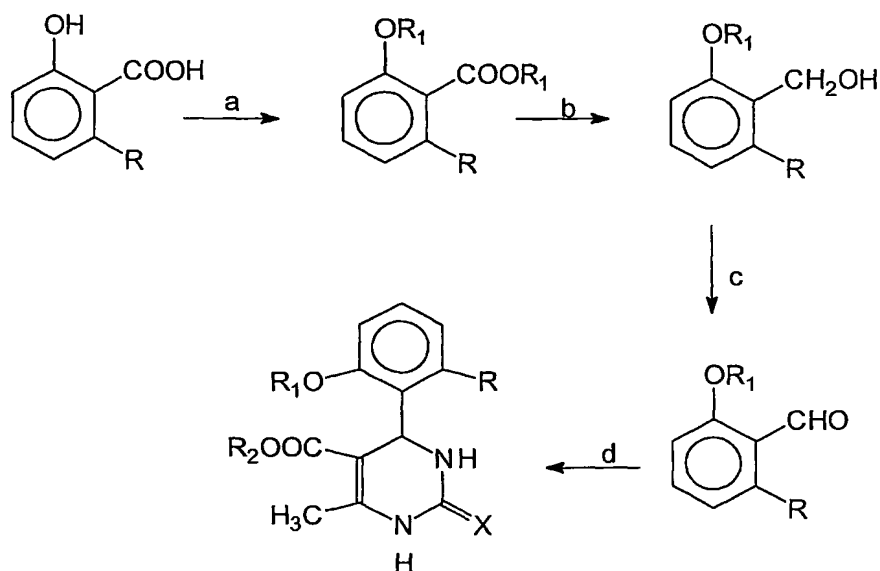
[0139] As indicated above, the compounds and compositions of this invention are useful as calcium entry blockers, and thus have broad pharmacological utility in that they exhibit (i) pronounced and long-lasting vasodilating effect accompanied by an energy-sparing effect on cardiac metabolism; (ii) antiarrhythmic and antianginal action on cardiac muscle; (iii) vascular spasmolytic action; (iv) antihypertensive action; (v) spasmolytic action on the smooth muscle of the gastrointestinal and urogenital tracts and the cerebrovascular and respiratory systems; (vi) as antihypercholesterolemic and antilipidemic agents; (vii) protection of the ischemic myocardium; (viii) inhibit irritable bowel syndrome and esophagel spasm; (ix) inhibit migraine; and, (x) epilepsy. Some of are also useful cardiotonic agents. This list also includes any cardiovascular problems related to low voltage activated (LVA) and high voltage activated (HVA) calcium channels.

[0140] The representative compounds of the present invention might inhibit vascular calcium contraction, reduce cardiac contractile force, inhibit calcium mediated tracheal contraction, inhibit calcium uptake in pituitary cells, or displace tritiated nitrendipine from membrane.

VI. Synthesis of the Compounds of Formula II

[0141] The compounds of the present invention can be divided into two general categories: those with a substitution at a nitrogen (either position 1 or position 3) of the pyrimidine ring and those without any substitution at that point, i.e., where that position is occupied by -NH. Scheme 1, below, shows the synthetic procedure for synthesizing compounds without N-substitution.

Scheme 1



X = O, S

R = alkyl chain (as described in claims)

a. dialkyl sulphate, K_2CO_3 , acetone, reflux 4hrs

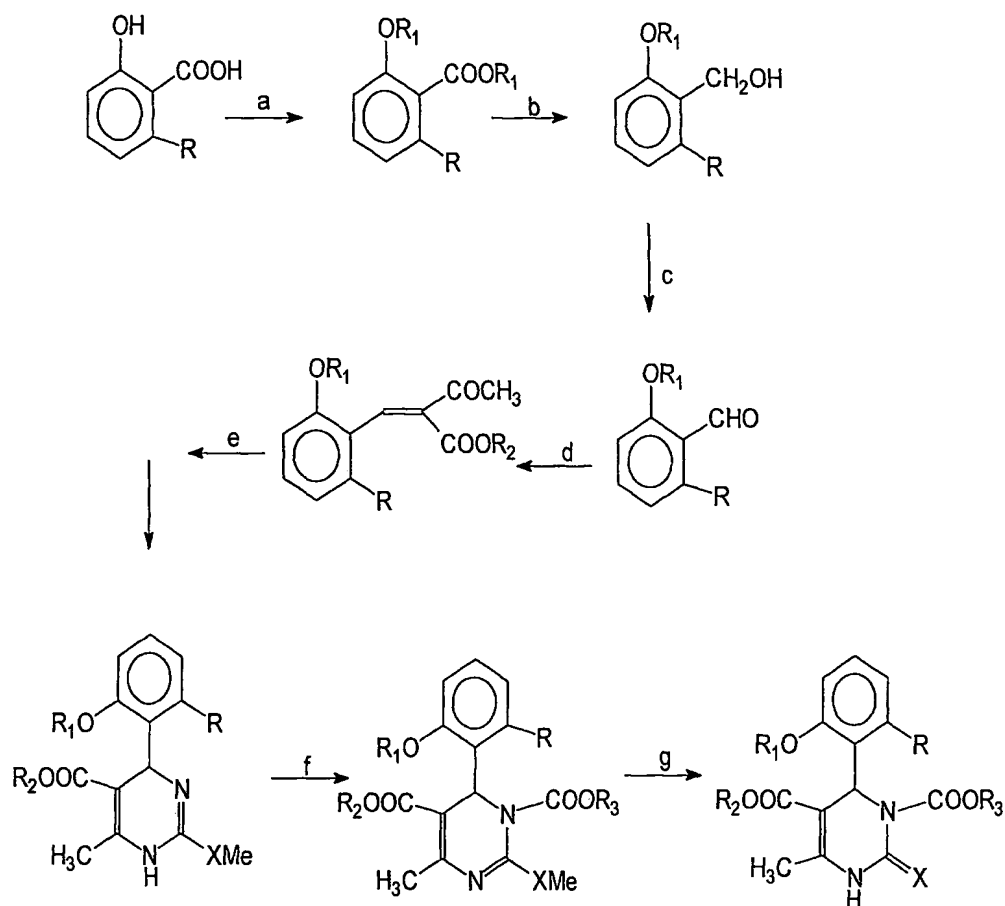
b. $LiAlH_4$, tetrahydrofuran, reflux, 3 hrs

c. pyridinium chloro chromate, dichloromethane, rt 3 hrs

d. appropriate acetoacetate, $BF_3 \cdot O(Et)_2$, (Urea or ThioUrea), tetrahydrofuran

[0142] Scheme 2 shows the synthetic procedure for synthesizing compounds that are substituted at the ring nitrogen ortho to the phenyl group.

Scheme 2



X = O,S

R = alkyl chain (as described in claims)

- a. dialkyl sulphate, K_2CO_3 , acetone, reflux 4hrs
- b. $LiAlH_4$, tetrahydrofuran, reflux, 3 hrs
- c. pyridinium chloro chromate, dichloromethane, rt 3 hrs
- d. appropriate acetoacetate, acetic acid, piperidine, isopropyl alcohol, rt 4-6 hrs
- e. appropriately substituted urea or thiourea, sodium bicarbonate, dimethyl formamide, heat at 60 °C for 6-8 hrs
- f. appropriately substituted chloroformate, pyridine, dichloromethane
- g. pyridine, dichloromethane (for X=O)
- g. trifluoro acetic acid, ethane thiol, dichloromethane, rt 12 hrs (for X= S)

Examples

[0143] The examples below are illustrative of some of the embodiments of the invention only and should not be construed to limit the scope of the claims.

Example 1: Extraction of ene mixture of anacardic acid (2-hydroxy-6-pentadecyl benzoic acid) from solvent extracted CNSL

[0144] Commercially available solvent extracted cashew nut shell liquid (CNSL) (100 g) was dissolved in 5% aqueous methanol (600 mL). To the methanolic solution was added activated charcoal (20 g), stirred for 15 minutes, then filtered over celite bed to remove any insoluble material. The clear filtrate was transferred into three neck round bottom flask fitted with a double surface reflux condenser and mechanical stirrer. Calcium hydroxide (50 g) was added in portions at room temperature and the reaction mass temperature was raised to 50 °C and allowed to maintain for 3 hrs. Progress of the reaction was monitored by thin layer chromatography (TLC) using hexane-ethyl acetate (8:2) as mobile phase. After the completion of reaction, the precipitated calcium anacardate was filtered and washed thoroughly with methanol (200 mL). The resultant cake was dried under vacuum at 45-50 °C for 2 hrs to yield calcium anacardate (120 g).

[0145] Dry cake (120 g) was suspended in distilled water (440 mL), added concentrated hydrochloric acid (33%, 60 mL) and stirred for 1 hr. Resultant solution was extracted with ethylacetate (2 X 150 mL). The combined organic layer was washed with distilled water (2 X 500 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield an ene mixture of anacardic acid. (Yield: 60 g).

Example 2: Hydrogenation of anacardic acid ene mixture

[0146] Anacardic acid ene mixture (30 g,) was dissolved in methanol (120 ml). 5% Pd/C (0.75 g, 2.5%) was added slowly and this solution were transferred to 250-mL hydrogenation flask. Initially the solution was flushed with nitrogen and then with hydrogen. Hydrogenation was carried out with 2.5 kg/cm² hydrogen gas pressure for 2 hrs. Then the solution was filtered through a celite bed to obtain catalyst free solution. This was evaporated under vacuum to get crude saturated anacardic acid. It was then recrystallised from petroleum ether (Yield: 25 g).

Example 3: Synthesis of ethyl 2-ethoxy-6-pentadecyl- benzoate:

[0147] Anacardic acid (10.11 g, 29 mmol) was dissolved in acetone (60 mL) and potassium carbonate (4.0 g, 29 mmol) was charged. Diethyl sulfate (8.93 g, 58 mmol) was added slowly under stirring. This solution was then transferred to a three-neck flask fitted with a reflux condenser and mechanical stirrer, and refluxed for 4 hrs. Progress of reaction was monitored by TLC (mobile phase:Hexane:EtOAc 9:1). After completion of reaction, it was filtered and acetone was evaporated under vacuum. Crude product was dissolved in dichloromethane (50 mL) and washed with water (2 X 50 mL), 5% sodium bicarbonate solution (50 mL), saturated brine (50 mL) and finally with distilled water (2 X 50 mL). The organic layer was dried over anhydrous sodium

sulphate, and evaporated under vacuum to give ethyl 2-ethoxy-6-pentadecyl- benzoate as oil. This was then dissolved in minimum amount of petroleum ether (40-60 °C) and cooled to 0 °C to give light brownish crystals (Yield: 12 g).

Example 4: Synthesis of isopropyl 2-isopropoxy-6-pentadecyl- benzoate:

[0148] Anacardic acid (10.11 g, 29 mmol) was dissolved in isobutyl methyl ketone (60 mL). To this, finely powdered potassium carbonate (4.0 g, 29 mmol) and benzyl tributyl ammonium chloride (1 g) was added. Slowly, isopropyl bromide (7.13 g, 58 mmol) was added and refluxed for 8 hrs. TLC was checked in hexane:EtOAc (9:1). Solution was filtered and evaporated under vacuum to give a viscous liquid. Crude product was dissolved in dichloromethane (50 mL) and washed with water (2 X 50 mL), 5% sodium bicarbonate solution (50 mL), saturated brine (50 mL) and finally with water (2 X 50 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated under vacuum to give isopropyl 2-isopropoxy-6-pentadecyl- benzoate as oil (Yield: 12 g).

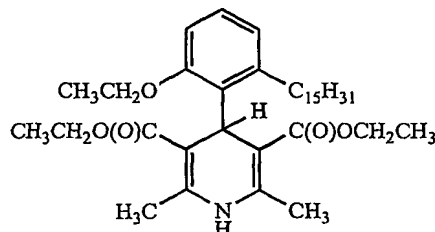
Example 5: Synthesis of 2-ethoxy-6-pentadecyl-benzyl alcohol:

[0149] Ethyl 2-ethoxy-6-pentadecyl-benzoate (10.9 g, 27 mmol) was dissolved in dry tetrahydrofuran (60 mL). This solution was transferred to dry 250 mL three neck round bottom flask fitted with reflux condenser, mechanical stirrer and it was maintained under nitrogen atmosphere through out the reaction. To this lithium aluminum hydride (2.04 g, 54 mmol) was added slowly. Reaction was highly exothermic. After addition the solution was slowly brought to the reflux temperature and maintained at that temperature for about two hours and TLC was checked in hexane:EtOAc (8:2). After completion of reaction, excess lithium aluminium hydride was decomposed by drop-wise addition of ethylacetate (80 mL). To this 5 M HCl (100 mL) was added and organic layer was separated, dried over anhydrous sodium sulphate, concentrated under vacuum to give a light brownish solid. This was recrystallised from petroleum ether (40-60 °C) to give white solid. Yield: 8 g.

Example 6: Synthesis of 2-ethoxy-6-pentadecyl-benzaldehyde

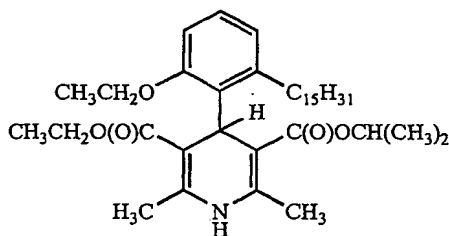
[0150] To a 250 mL round bottom flask fitted with a reflux condenser, was added pyridinium chloro chromate (PCC) (16.1 g, 75 mmol) in anhydrous dichloromethane (100 mL). 2-Ethoxy-6-pentadecyl-benzyl alcohol (18.1 g, 50 mmol) in dichloromethane (10 mL) was added in one portion to the magnetically stirred solution. After 1.5 hr dry ether (100 mL) was added and the supernatant decanted from the black gum. The insoluble residue was washed thoroughly with diethyl ether (3 X 25 mL), where upon it became black granular solid. The organic solution was passed through a short pad of celite, and the solvent was removed by distillation to obtain brownish low melting solid (Yield: 15 g).

Example 7: Synthesis of diethyl 1,4-dihydro-4-(2'-ethoxy-6'-pentadecyl phenyl)-2,6-dimethyl-3,5- pyridine dicarboxylate



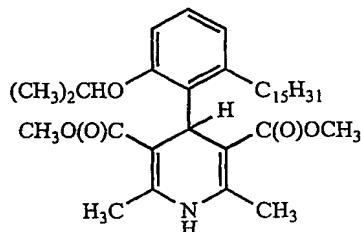
[0151] 2-Ethoxy-6-pentadecyl benzaldehyde (3 g, 8.3 mmol) and ethyl acetoacetate (1.08 g, 8.3 mmol) were dissolved in n-butanol (20 mL). Acetic acid (0.5 g, 8.3 mmol) and piperidine (0.7 g, 8.3 mmol) were added and stirred at room temperature for 3-4 hrs. Ethyl-3-amino crotonate (1.08 g, 8.3 mmol) was then added and refluxed for 10 hrs. n-Butanol was evaporated and reaction mixture was washed with distilled water and extracted with dichloromethane (10 mL). Organic layer was dried over sodium sulfate, evaporated and compound was purified by column chromatography using silicagel (100-200 mesh) with hexane:EtOAc (94:6) solvent system to give diethyl 1,4-dihydro-4-(2'-ethoxy-6'-pentadecyl phenyl) -2,6-dimethyl-3,5- pyridine dicarboxylate as white powder.

Example 8: Synthesis of ethyl isopropyl 1,4-dihydro-4-(2'-ethoxy-6'-pentadecylphenyl)-2,6-dimethyl-3,5- pyridine dicarboxylate



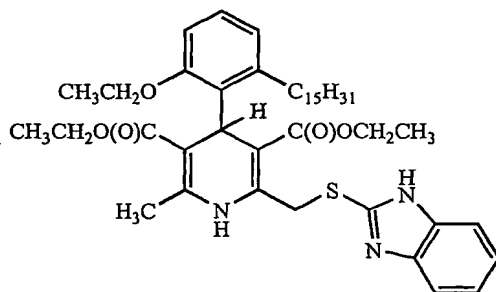
[0152] 2-Ethoxy-6-pentadecyl benzaldehyde (3 g, 8.3 mmol) and isopropyl acetoacetate (1.19 g, 8.3 mmol) were dissolved in n-butanol (20 mL). Acetic acid (0.5 g, 8.3 mmol) and piperidine (0.7 g, 8.3 mmol) were added and stirred at room temperature for 3-4 hrs. Ethyl-3-amino crotonate (1.08 g, 8.3 mmol) was then added and refluxed for 10 hrs. n-Butanol was evaporated and reaction mixture was washed with distilled water and extracted with dichloromethane (10 mL). Organic layer was dried over sodium sulfate, evaporated and compound was purified by column chromatography using silica gel (100-200 mesh) with hexane:EtOAc (94:6) solvent system to give ethyl isopropyl 1,4-dihydro-4-(2'-ethoxy-6'-pentadecylphenyl) -2,6-dimethyl-3,5- pyridine dicarboxylate as viscous liquid .

Example -9: Synthesis of dimethyl 1,4-dihydro-4-(2'-isopropoxy-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate



[0153] 2-Isopropoxy-6-pentadecyl benzaldehyde (3.1 g, 8.3 mmol) and methyl acetoacetate (0.96 g, 8.3 mmol) were dissolved in n-butanol (20 mL). Acetic acid (0.5 g, 8.3 mmol) and piperidine (0.7 g, 8.3 mmol) were added and stirred at room temperature for 3-4 hrs. methyl-3-amino crotonate (0.97 g, 8.3 mmol) was then added and refluxed for 10 hrs. n-Butanol was evaporated and reaction mixture was washed with distilled water and extracted with dichloromethane (10 mL). Organic layer was dried over sodium sulfate, evaporated and compound was purified by column chromatography using silicagel (100-200 mesh) with hexane:EtOAc (94:6) solvent system to give dimethyl 1,4-dihydro-4-(2'-isopropoxy-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate as viscous liquid.

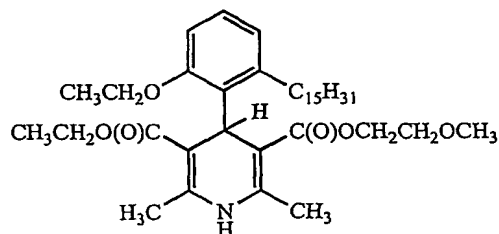
Example 10: Synthesis of diethyl 1,4-dihydro-4-(2'-ethoxy-6'-pentadecyl phenyl)-6-methyl-2-(2'-mercapto-1'H-benzimidazolyl) methyl-3,5-pyridine dicarboxylate



[0154] 2-Ethoxy-6-pentadecylbenzaldehyde (3 g, 8.3 mmol) and 4-chloro ethyl acetoacetate (1.36 g, 8.3 mmol) were dissolved in n-butanol (20 mL). Acetic acid (0.5 g, 8.3 mmol) and piperidine (0.7 g, 8.3 mmol) were added and stirred at room temperature for 3-4 hrs. Ethyl-3-amino crotonate (1.08 g, 8.3 mmol) was then added and refluxed for 10 hrs. n-Butanol was evaporated and reaction mixture was washed with distilled water and extracted with dichloromethane (10 mL). Organic layer was dried over sodium sulfate, evaporated and compound was purified by column chromatography using silicagel (100-200 mesh) with hexane:EtOAc (94:6) solvent system to give diethyl 1,4-dihydro-4-(2'-ethoxy-6'-pentadecylphenyl)-6-methyl-2-chloromethyl-3,5-pyridine dicarboxylate. This compound (0.6 g, 1.2 mmol) was dissolved in

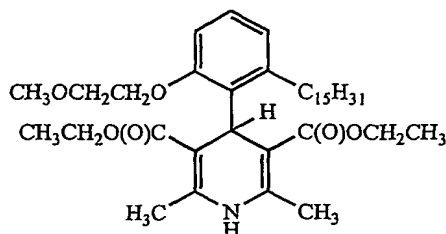
dichloromethane (10 mL) and then 2-mercapto-1H-benzimidazole (0.18 g, 1.2 mmol) and NaOH (0.048 g, 1.2 mmol) were charged. Catalytic amount of tetrabutyl ammonium bromide was added and magnetically stirred at room temperature for 2 hrs. The final compound was purified by column chromatography as mentioned in Example 7.

Example 11: Synthesis of ethyl 2-methoxyethyl 1,4-dihydro-4-(2'-ethoxy-6'-pentadecylphenyl)-2,6-dimethyl-3,5 pyridine dicarboxylate



[0155] 2-Ethoxy-6-pentadecyl benzaldehyde (3 g, 8.3 mmol) and methoxy ethyl acetoacetate (1.32 g, 8.3 mmol) were dissolved in n-butanol (20 mL). Acetic acid (0.5 g, 8.3 mmol) and piperidine (0.7 g, 8.3 mmol) were added and stirred at room temperature for 3-4 hrs. Ethyl-3-amino crotonate (1.08 g, 8.3 mmol) was then added and refluxed for 10 hrs. n-Butanol was evaporated and reaction mixture was washed with distilled water and extracted with dichloromethane (10 mL). Organic layer was dried over sodium sulfate, evaporated and compound was purified by column chromatography using silicagel (100-200 mesh) with hexane:EtOAc (94:6) solvent system to give ethyl 2-methoxyethyl 1,4-dihydro-4-(2'-ethoxy-6'-pentadecylphenyl)-2,6-dimethyl-3,5 pyridine dicarboxylate.

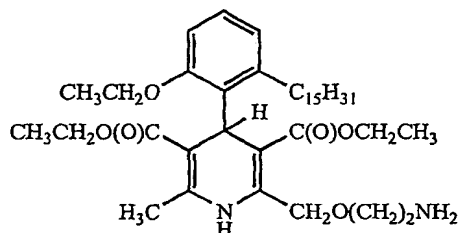
Example 12: Synthesis of diethyl 1,4-dihydro-4-(2'-(2''methoxy) ethoxy-6'-pentadecylphenyl)-2,6-dimethyl-3,5- pyridine dicarboxylate



[0156] 2-(2'-methoxyethoxy)-6-pentadecyl benzaldehyde (3.2 g, 8.3 mmol) and ethyl acetoacetate (1.08 g, 8.3 mmol) were dissolved in n-butanol (20 mL). Acetic acid (0.5 g, 8.3 mmol) and piperidine (0.7 g, 8.3 mmol) were added and stirred at room temperature for 3-4 hrs. Ethyl-3-amino crotonate (1.08 g, 8.3 mmol) was then added and refluxed for 10 hrs. n-Butanol was evaporated and reaction mixture was washed with distilled water and extracted with dichloromethane (10 mL). Organic layer was dried over sodium sulfate, evaporated and compound was purified by column chromatography using silicagel (100-200 mesh) with hexane:EtOAc (94:6)

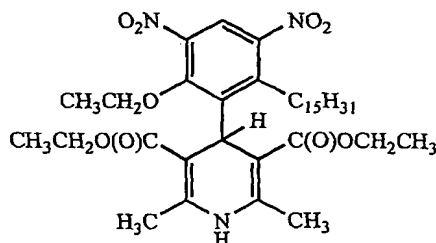
solvent system to give diethyl 1,4-dihydro-4-(2'-(2''methoxy)ethoxy-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate.

Example 13: Synthesis of diethyl 1,4-dihydro-4-(2'-ethoxy-6'-pentadecylphenyl)-2-((2'-amino ethoxy)methyl)-6-methyl-3,5-pyridine dicarboxylate



[0157] 2-Ethoxy-6-pentadecyl benzaldehyde (3 g, 8.3 mmol) and 4-chloro ethyl acetoacetate (1.36 g, 8.3 mmol) were dissolved in n-butanol (20 mL). Acetic acid (0.5 g, 8.3 mmol) and piperidine (0.7 g, 8.3 mmol) were added and stirred at room temperature for 3-4 hrs. Ethyl-3-amino crotonate (1.08 g, 8.3 mmol) was then added and refluxed for 10 hrs. n-Butanol was evaporated and reaction mixture was washed with distilled water and extracted with dichloromethane (10 mL). Organic layer was dried over sodium sulfate, evaporated and compound was purified by column chromatography using silicagel (100-200 mesh) with hexane:EtOAc (94:6) solvent system to give diethyl 1,4-dihydro-4-(2'-ethoxy-6'-pentadecylphenyl)-2-chloromethyl-6-methyl-3,5-pyridine dicarboxylate). This compound (0.6 g, 1 mmol) was dissolved in dichloromethane (10 mL) and 2-amino ethanol (0.061 g, 1 mmol) and KOH (0.06 g, 1 mmol) were added and stirred magnetically for 15 min. Then catalytic amount of dibenzo- 18-crown-6 and tetrabutyl ammonium bromide was added and stirred for one hour. Then the product was purified by column chromatography as mentioned in example 7.

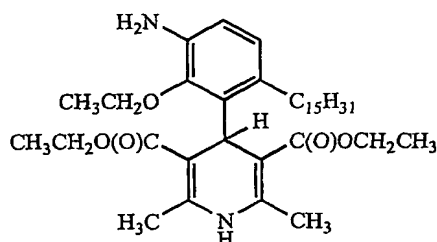
Example 14: Synthesis of diethyl 1,4-dihydro-4-(2'-ethoxy-3',5'-dinitro-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate



[0158] 2-Ethoxy-3,5-dinitro-6-pentadecyl benzaldehyde (3.73 g, 8.3 mmol) and ethyl acetoacetate (1.08 g, 8.3 mmol) were dissolved in n-butanol (20 mL). Acetic acid (0.5 g, 8.3 mmol) and piperidine (0.7 g, 8.3 mmol) were added and stirred at room temperature for 3-4 hrs. Ethyl-3-amino crotonate (1.08 g, 8.3 mmol) was then added and refluxed for 10 hrs. n-Butanol was evaporated and reaction mixture was washed with distilled water and extracted with

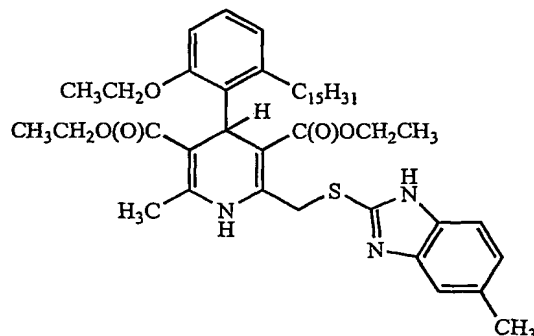
dichloromethane (10 mL). Organic layer was dried over sodium sulfate, evaporated and compound was purified by column chromatography using silicagel (100-200 mesh) with hexane:EtOAc (94:6) solvent system to give diethyl 1,4-dihydro-4-(2'-ethoxy-3',5'-dinitro-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate.

Example 15: Synthesis of diethyl 1,4-dihydro-4-(2'-ethoxy-3'-amino-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate



[0159] 2-Ethoxy-3-acetanilido-6-pentadecyl benzaldehyde (3.46 g, 8.3 mmol) and ethyl acetoacetate (1.08 g, 8.3 mmol) were dissolved in n-butanol (20 mL). Acetic acid (0.5 g, 8.3 mmol) and piperidine (0.7 g, 8.3 mmol) were added and stirred at room temperature for 3-4 hrs. Ethyl-3-amino crotonate (1.08g, 8.3 mmol) was then added and refluxed for 10 hrs. n-Butanol was evaporated and reaction mixture was washed with distilled water and extracted with dichloromethane (10 mL). Organic layer was dried over sodium sulfate, evaporated and compound was hydrolysed and purified by column chromatography using silicagel (100-200 mesh) with hexane:EtOAc (94:6) solvent system to give diethyl 1,4-dihydro-4-(2'-ethoxy-3'-amino-6'-pentadecylphenyl)-2,6-dimethyl-3,5-pyridine.

Example 16: Synthesis of diethyl 1,4-dihydro-4-(2'-ethoxy-6'-pentadecyl phenyl)-6-methyl-2-(5''-methyl-2'-mercapto-1'H-benzimidazolyl)methyl-3,5-pyridine dicarboxylate



[0160] 2-Ethoxy-6-pentadecyl benzaldehyde (3 g, 8.3 mmol) and 4-chloro ethyl acetoacetate (1.36 g, 8.3 mmol) were dissolved in n-butanol (20 mL). Acetic acid (0.5 g, 8.3 mmol) and piperidine (0.7 g, 8.3 mmol) were added and stirred at room temperature for 3-4 hrs. Ethyl-3-amino crotonate (1.08 g, 8.3 mmol) was then added and refluxed for 10 hrs. n-Butanol was

evaporated and reaction mixture was washed with distilled water and extracted with dichloromethane (10 mL). Organic layer was dried over sodium sulfate, evaporated and compound was purified by column chromatography using silicagel (100-200 mesh) with hexane:EtOAc (94:6) solvent system to give diethyl 1,4-dihydro-4-(2'-ethoxy-6'-pentadecylphenyl)-6-methyl-2-chloromethyl-3,5-pyridine dicarboxylate. This compound (0.6 g, 1 mmol) was dissolved in dichloromethane (10 mL) and then (5'-methyl) 2-mercapto-1H-benzimidazole (0.164 g, 1 mmol) and NaOH (0.04 g, 1 mmol) were charged. Catalytic amount of tetrabutyl ammonium bromide and dibenzo-18-crown-6 were added and magnetically stirred at room temperature for 2 hrs. The final compound was purified by column chromatography as mentioned in Example 7.

Example 17: Synthesis of 1,4-dihydro-2-[[[4-methoxyphenyl)methyl]thio]-6-methyl-4-[2-methoxy-6-pentadecylphenyl]-5-pyrimidinecarboxylic acid ethyl ester.

[0161] The reaction mixture containing 2-[[2-methoxy-6-pentadecyl phenyl]methylene]-3-oxobutanoic acid ethyl ester (3 g, 6.6 mmol), 2-((4-methoxyphenyl) methyl)-2-thiopseudourea hydrochloride (1.2 g, 6.6 mmol), and sodium acetate (0.6 g, 7 mmol) in dimethylformamide (30 mL) was heated at 70 °C for 4 h. The reaction was cooled to room temperature, diluted with ether, and filtered. The filtrate was washed with water, sodium bicarbonate, and brine and dried over anhydrous sodium sulfate. The solvent was evaporated, and the compound was obtained as brown viscous liquid.

Example 18: Synthesis of 1,4-dihydro-2-[[[4-methoxyphenyl)methyl]oxy]-6-methyl-4-[2-methoxy-6-pentadecylphenyl]-5-pyrimidinecarboxylic acid ethyl ester

[0162] The reaction mixture containing 2-[[2-methoxy-6-pentadecyl phenyl]methylene]-3-oxobutanoic acid ethyl ester (3 g, 6.6 mmol), 2-((4-methoxyphenyl) methyl)-2-oxypseudourea hydrochloride (1.1 g, 6.6 mmol), and sodium acetate (0.6 g, 7 mmol) in dimethylformamide (30 mL) was heated at 70 °C for 4 h. The reaction was cooled to room temperature, diluted with ether, and filtered. The filtrate was washed with water, sodium bicarbonate, and brine and dried over anhydrous sodium sulfate. The solvent was evaporated, and the compound was obtained as brown viscous liquid.

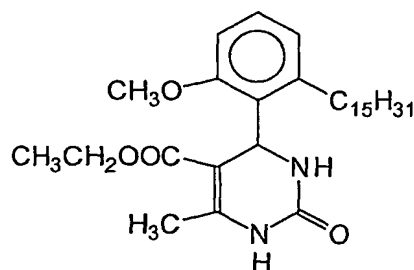
Example 19: 5-ethoxycarbonyl-4-(2-ethoxy-6-pentadecylphenyl)-6-(2'-mercapto-1'H-benzimidazolyl) methyl-3,4-dihydropyrimidin-2(1H)-one (PPK-21)

[0163] A solution of 4(2'-mercapto-1'H-benzimidazolyl) ethylacetoacetate (2.3 g, 8.3 mmol), 2-ethoxy-6-pentadecyl benzaldehyde (3 g, 8.3 mmol) and urea (1.0 g, 16.6 mmol) in tetrahydrofuran (20 mL) was heated to reflux (65-70 °C) in the presence of hydrochloric acid (30%) for 7 h. The reaction mixture after being cooled to room temperature was poured into crushed ice (20 g) and stirred for 5 min. The viscous liquid was extracted with ethylacetate (40 mL) and was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent was evaporated to yield light yellow oil. This crude product

was purified by flash column chromatography and recrystallised from hexane to get white crystalline solid of title compound.

- [0164] Melting point : 87-88 °C
 [0165] IR (cm⁻¹) : 3425 (N-H), 2920 (C-H), 1694 (C=O)
 [0166] Mass (Electrospray): 663 (M+1), 661 (M-1)
 [0167] ¹H NMR (δ ppm) : 8.5 (bs, 1H, D₂O exchangeable, N-H) 7.7 (d, J=6 Hz, 1H, Aromatic proton) 7.5 (m, 1H, Aromatic proton) 7.25 (m, 3H, Aromatic proton, N-H, D₂O exchangeable) 7.15 (t, J=8 Hz, 1H, Aromatic proton) 6.85 (d, J=8Hz, 2H, Aromatic proton) 5.8 (s, 1H, C₄-H) 4.6 (s, 1H, D₂O exchangeable, N-H) 4.5 (s, 2H, S-CH₂) 4.0 (m, J=6 Hz, 4H, O-CH₂) 3.1 (m, 1H, benzylic) 2.5 (m, 1H, benzylic) 1.85-1.1 (m, 35H, (CH₂)₁₃ from alkyl chain, CH₃, CH₃, allylic CH₃) 0.9 (dt, 3H, terminal CH₃ from alkyl chain).

Example 20: 5-ethoxycarbonyl-4-(2-methoxy-6-pentadecylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (PPK-22)



[0168] A solution of ethylacetoacetate (1.13 g, 8.6 mmol), 2-methoxy-6-pentadecyl benzaldehyde (3 g, 8.6 mmol) and urea (1.04 g, 17.3 mmol) in tetrahydrofuran (20 mL) was heated to reflux (65-70 °C) in the presence of hydrochloric acid (30%) for 7 h. The reaction mixture after being cooled to room temperature was poured into crushed ice (20 g) and stirred for 5 min. The viscous liquid was extracted with ethylacetate (40 mL) and was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent was evaporated to yield light yellow oil. This crude product was purified by flash column chromatography and recrystallised from hexane to get white crystalline solid of title compound.

- [0169] Melting point : 91-93 °C
 [0170] IR (cm⁻¹) : 3420 (N-H), 2922 (C-H), 1690 (C=O)
 [0171] Mass (Electrospray): 501 (M+1), 499 (M-1)
 [0172] ¹H NMR (δ ppm) : 7.6 (bs, 1H, D₂O exchangeable, N-H) 7.15 (t, J=8 Hz, 1H, aromatic proton) 6.85 (d, J=8Hz, 2H, aromatic protons) 5.95 (s, 1H, C₄-H) 4.95 (s, 1H, D₂O exchangeable, N-H) 4.0 (m, 2H, O-CH₂) 3.8 (s, 3H, O-CH₃) 3.15 (m, 1H, benzylic) 2.5 (m, 1H,

benzylic) 2.25 (s, 3H, allylic) 1.85-0.95 (m, 29H, (CH₂)₁₃ from alkyl chain, CH₃) 0.9 (dt, 3H, terminal CH₃ from alkyl chain).

[0173] bs-broad singlet, t-triplet, d-doublet, s-singlet, m-multiplet, dt-distorted triplet.

Example 21: 5-methoxycarbonyl-4-(2-ethoxy-6-pentadecylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (PPK-23)

[0174] A solution of methylacetoacetate (1.2 g, 8.5 mmol), 2-ethoxy-6-pentadecyl benzaldehyde (3 g, 8.5 mmol) and urea (1.00 g, 17 mmol) in tetrahydrofuran (20 mL) was heated to reflux (65-70 °C) in the presence of hydrochloric acid (30%) for 7 h. The reaction mixture after being cooled to room temperature was poured into crushed ice (20 g) and stirred for 5 min. The viscous liquid was extracted with ethylacetate (40 mL) and was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent was evaporated to yield light yellow oil. This crude product was purified by flash column chromatography and recrystallized from hexane to get white crystalline solid of title compound.

[0175] Melting point : 127-129 °C

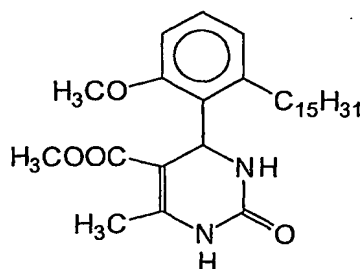
[0176] IR (cm⁻¹) : 3426 (N-H), 2920 (C-H), 1694 (C=O)

[0177] Mass (Electrospray): 501 (M+1), 499 (M-1)

[0178] ¹H NMR (δ ppm) : 7.6 (bs, 1H, D₂O exchangeable, N-H) 7.1 (t, J=8 Hz, 1H, aromatic proton) 6.72 (d, J=8Hz, 2H, aromatic protons) 5.8 (s, 1H, C₄-H) 4.8 (s, 1H, D₂O exchangeable, N-H) 4.0 (q, 2H, J=6 Hz, O-CH₂) 3.5 (s, 3H, O-CH₃) 3.1 (m, 1H, benzylic) 2.5 (m, 1H, benzylic) 2.3 (s, 3H, allylic) 1.8-1.1 (m, 29H, (CH₂)₁₃ from alkyl chain, CH₃) 0.85 (dt, 3H, terminal CH₃ from alkyl chain).

[0179] bs-broad singlet, t-triplet, d-doublet, s-singlet, m-multiplet, dt-distorted triplet, q-quartet.

Example 22: 5-methoxycarbonyl-4-(2-methoxy-6-pentadecylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (PPK-24)



[0180] A solution of methylacetoacetate (1.2 g, 8.5 mmol), 2-methoxy-6-pentadecyl benzaldehyde (3.1 g, 8.5 mmol) and urea (1.00 g, 17 mmol) in tetrahydrofuran (20 mL) was heated to reflux (65-70 °C) in the presence of hydrochloric acid (30%) for 7 h. The reaction mixture after

being cooled to room temperature was poured into crushed ice (20 g) and stirred for 5 min. The viscous liquid was extracted with ethylacetate (40 mL) and was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent was evaporated to yield light yellow oil. This crude product was purified by flash column chromatography and recrystallized from hexane to get white crystalline solid of title compound.

[0181] Melting point : 101-102 °C

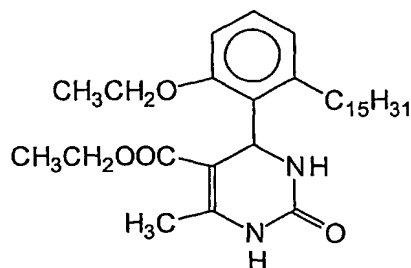
[0182] IR (cm⁻¹) : 3425 (N-H), 2918 (C-H), 1690 (C=O)

[0183] Mass (Electrospray): 487 (M+1), 485 (M-1)

[0184] ¹H NMR (δ ppm) : 7.6 (bs, 1H, D₂O exchangeable, N-H) 7.15 (t, J=8 Hz, 1H, aromatic proton) 6.73 (d, J=8Hz, 2H, aromatic protons) 5.8 (s, 1H, C₄-H) 4.8 (s, 1H, D₂O exchangeable, N-H) 3.78 (s, 3H, O-CH₂) 3.6 (s, 3H, O-CH₃) 3.1 (m, 1H, benzylic) 2.5 (m, 1H, benzylic) 2.3 (s, 3H, allylic) 1.8-1.1 (m, 26H, (CH₂)₁₃ from alkyl chain) 0.85 (dt, 3H, terminal CH₃ from alkyl chain).

[0185] bs-broad singlet, t-triplet, d-doublet, s-singlet, m-multiplet, dt-distorted triplet, q-quartet.

Example 23: 5-ethoxycarbonyl-4-(2-ethoxy-6-pentadecylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (PPK-25)



[0186] A solution of ethylacetoacetate (1.25 g, 8.5 mmol), 2-ethoxy-6-pentadecyl benzaldehyde (3 g, 8.5 mmol) and urea (1.1 g, 17 mmol) in tetrahydrofuran (20 mL) was heated to reflux (65-70 °C) in the presence of hydrochloric acid (30%) for 7 h. The reaction mixture after being cooled to room temperature was poured into crushed ice (20 g) and stirred for 5 min. The viscous liquid was extracted with ethylacetate (40 mL) and was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent was evaporated to yield light yellow oil. This crude product was purified by flash column chromatography and recrystallized from hexane to get white crystalline solid of title compound.

[0187] Melting point : 99-100 °C

[0188] IR (cm⁻¹) : 3420 (N-H), 2924 (C-H), 1690 (C=O)

[0189] Mass (Electrospray): 515 (M+1), 513 (M-1)

[0190] ^1H NMR (8 ppm) : 7.35 (bs, 1H, D_2O exchangeable, N-H) 7.15 (t, $J=8$ Hz, 1H, aromatic proton) 6.72 (d, $J=8$ Hz, 2H, aromatic protons) 5.8 (s, 1H, $\text{C}_4\text{-H}$) 4.75 (s, 1H, D_2O exchangeable, N-H) 4.0 (m, 4H, O-CH_2) 3.15 (m, 1H, benzylic) 2.45 (m, 1H, benzylic) 2.3 (s, 3H, allylic) 1.8-1.1 (m, 32H, $(\text{CH}_2)_{13}$ from alkyl chain, CH_3 , CH_3) 0.9 (dt, 3H, terminal CH_3 from alkyl chain).

[0191] bs-broad singlet, t-triplet, d-doublet, s-singlet, m-multiplet, dt-distorted triplet

Example 24: 5-methoxycarbonyl-4-(2-methoxy-6-(8' Z, 11' Z, 14' Z) pentadecatrienyl phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (PPK-26A)

[0192] A solution of methylacetoacetate (1.2 g, 8.5 mmol), 2-methoxy-6-(8' Z, 11' Z, 14' Z) pentadecatrienyl benzaldehyde (3.1 g, 8.5 mmol) and urea (1.00 g, 17 mmol) in tetrahydrofuran (20 mL) was heated to reflux (65-70 °C) in the presence of hydrochloric acid (30%) for 7 h. The reaction mixture after being cooled to room temperature was poured into crushed ice (20 g) and stirred for 5 min. The viscous liquid was extracted with ethylacetate (40 mL) and was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent was evaporated to yield light yellow oil. This crude product was purified by flash column chromatography and recrystallised from hexane to get white crystalline solid of title compound.

[0193] IR (cm^{-1}) : 3427 (N-H), 2922 (C-H), 1691 (C=O)

[0194] Mass (Electrospray): 481 (M+1), 479 (M-1)

Example 25: 5-methoxycarbonyl-4-(2-methoxy-6-(8' Z, 11' Z) pentadecadienyl phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (PPK-26B)

[0195] A solution of methylacetoacetate (1.2 g, 8.5 mmol), 2-methoxy-6-(8' Z, 11' Z) pentadecadienyl benzaldehyde (3.1 g, 8.5 mmol) and urea (1.00 g, 17 mmol) in tetrahydrofuran (20 mL) was heated to reflux (65-70 °C) in the presence of hydrochloric acid (30%) for 7 h. The reaction mixture after being cooled to room temperature was poured into crushed ice (20 g) and stirred for 5 min. The viscous liquid was extracted with ethylacetate (40 mL) and was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent was evaporated to yield light yellow oil. This crude product was purified by flash column chromatography.

[0196] IR (cm^{-1}) : 3426 (N-H), 2920 (C-H), 1690 (C=O)

[0197] Mass (Electrospray): 483 (M+1), 481 (M-1)

Example 26: 5-methoxycarbonyl-4-(2-methoxy-6-(8' Z) pentadecenyl phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (PPK-26C)

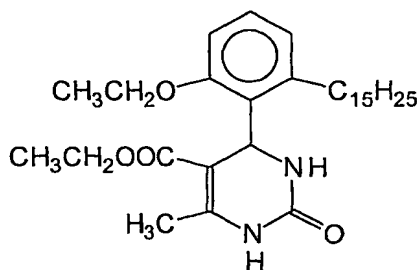
[0198] A solution of methylacetoacetate (1.2 g, 8.5 mmol), 2-methoxy-6-(8' Z) pentadecenyl benzaldehyde (3.1 g, 8.5 mmol) and urea (1.00 g, 17 mmol) in tetrahydrofuran (20

mL) was heated to reflux (65-70 °C) in the presence hydrochloric acid (30%) for 7 h. The reaction mixture after being cooled to room temperature was poured into crushed ice (20 g) and stirred for 5 min. The viscous liquid was extracted with ethylacetate (40 mL) and was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent was evaporated to yield light yellow oil. This crude product was purified by flash column chromatography.

[0199] IR (cm⁻¹) : 3424 (N-H), 2924 (C-H), 1692 (C=O)

[0200] Mass (Electrospray): 485 (M+1), 483 (M-1)

Example 27: 5-ethoxycarbonyl-4-(2-ethoxy-6-(8' Z, 11' Z, 14' Z) pentadecatrienyl phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (PPK-27A)

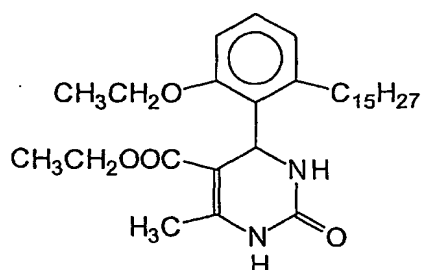


[0201] A solution of ethylacetoacetate (1.3 g, 8.5 mmol), 2-ethoxy-6-(8' Z, 11' Z, 14' Z) pentadecatrienyl benzaldehyde (3.2 g, 8.5 mmol) and urea (1.1 g, 17 mmol) in tetrahydrofuran (20 mL) was heated to reflux (65-70 °C) in the presence of hydrochloric acid (30%) for 7 h. The reaction mixture after being cooled to room temperature was poured into crushed ice (20 g) and stirred for 5 min. The viscous liquid was extracted with ethylacetate (40 mL) and was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent was evaporated to yield light yellow oil. This crude product was purified by flash column chromatography and recrystallised from hexane to get white crystalline solid of title compound.

[0202] IR (cm⁻¹) : 3422 (N-H), 2920 (C-H), 1690 (C=O)

[0203] Mass (Electrospray): 509 (M+1), 507 (M-1)

Example 28: 5-ethoxycarbonyl-4-(2-ethoxy-6-(8' Z, 11' Z) pentadecadienyl phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (PPK-27B)

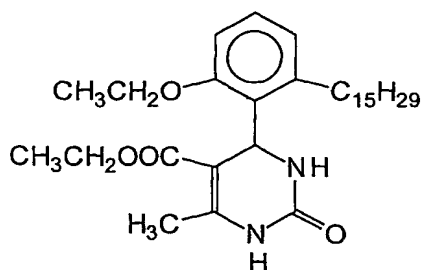


[0204] A solution of ethylacetoacetate (1.3 g, 8.5 mmol), 2-ethoxy-6-(8' Z, 11' Z) pentadecadienyl benzaldehyde (3.2 g, 8.5 mmol) and urea (1.1 g, 17 mmol) in tetrahydrofuran (20 mL) was heated to reflux (65-70 °C) in the presence of hydrochloric acid (30%) for 7 h. The reaction mixture after being cooled to room temperature was poured into crushed ice (20 g) and stirred for 5 min. The viscous liquid was extracted with ethylacetate (40 mL) and was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent was evaporated to yield light yellow oil. This crude product was purified by flash column chromatography.

[0205] IR (cm⁻¹) : 3424 (N-H), 2924 (C-H), 1691 (C=O)

[0206] Mass (Electrospray): 511 (M+1), 509 (M-1)

Example 29: 5-ethoxycarbonyl-4-(2-ethoxy-6-(8' Z) pentadecenyl phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (PPK-27C)



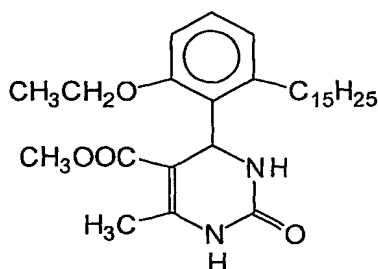
[0207] A solution of ethylacetoacetate (1.3 g, 8.5 mmol), 2-ethoxy-6-(8' Z) pentadecenyl benzaldehyde (3.2 g, 8.5 mmol) and urea (1.1 g, 17 mmol) in tetrahydrofuran (20 mL) was heated to reflux (65-70 °C) in the presence of hydrochloric acid (30%) for 7 h. The reaction mixture after being cooled to room temperature was poured into crushed ice (20 g) and stirred for 5 min. The viscous liquid was extracted with ethylacetate (40 mL) and was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium

sulfate, the solvent was evaporated to yield light yellow oil. This crude product was purified by flash column chromatography.

[0208] IR (cm^{-1}) : 3423 (N-H), 2923 (C-H), 1691 (C=O)

[0209] Mass (Electrospray): 513 (M+1), 511 (M-1)

Example 30: 5-methoxycarbonyl-4-(2-ethoxy-6-(8' Z, 11' Z, 14' Z) pentadecatrienyl phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (PPK-28A)

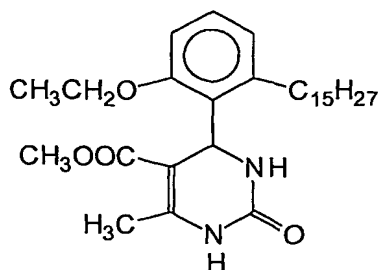


[0210] A solution of methylacetoacetate (1.2 g, 8.5 mmol), 2-ethoxy-6-(8' Z, 11' Z, 14' Z) pentadecatrienyl benzaldehyde (3.2 g, 8.5 mmol) and urea (1.1 g, 17 mmol) in tetrahydrofuran (20 mL) was heated to reflux (65-70 °C) in the presence of hydrochloric acid (30%) for 7 h. The reaction mixture after being cooled to room temperature was poured into crushed ice (20 g) and stirred for 5 min. The viscous liquid was extracted with ethylacetate (40 mL) and was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent was evaporated to yield light yellow oil. This crude product was purified by flash column chromatography and recrystallised from hexane to get white crystalline solid of title compound.

[0211] IR (cm^{-1}) : 3421 (N-H), 2920 (C-H), 1690 (C=O)

[0212] Mass (Electrospray): 495 (M+1), 493 (M-1)

Example 31: 5-methoxycarbonyl-4-(2-ethoxy-6-(8' Z, 11' Z) pentadecadienyl phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (PPK-28B)



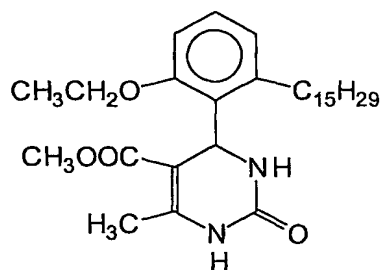
[0213] A solution of methylacetoacetate (1.2 g, 8.5 mmol), 2-ethoxy-6-(8' Z, 11' Z) pentadecadienyl benzaldehyde (3.2 g, 8.5 mmol) and urea (1.1 g, 17 mmol) in tetrahydrofuran (20

mL) was heated to reflux (65-70 °C) in the presence of hydrochloric acid (30%) for 7 h. The reaction mixture after being cooled to room temperature was poured into crushed ice (20 g) and stirred for 5 min. The viscous liquid was extracted with ethylacetate (40 mL) and was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent was evaporated to yield light yellow oil. This crude product was purified by flash column chromatography.

[0214] IR (cm⁻¹) : 3423 (N-H), 2921 (C-H), 1690 (C=O)

[0215] Mass (Electrospray): 497 (M+1), 495 (M-1)

Example 32: 5-methoxycarbonyl-4-(2-ethoxy-6-(8' Z) pentadecenyl phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (PPK-28C)

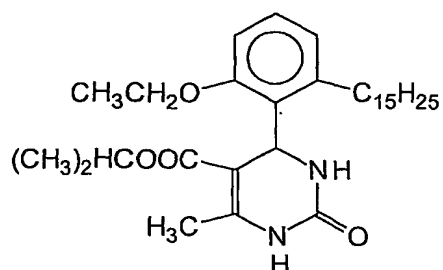


[0216] A solution of methylacetoacetate (1.2 g, 8.5 mmol), 2-ethoxy-6-(8' Z) pentadecenyl benzaldehyde (3.2 g, 8.5 mmol) and urea (1.1 g, 17 mmol) in tetrahydrofuran (20 mL) was heated to reflux (65-70 °C) in the presence of hydrochloric acid (30%) for 7 h. The reaction mixture after being cooled to room temperature was poured into crushed ice (20 g) and stirred for 5 min. The viscous liquid was extracted with ethylacetate (40 mL) and was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent was evaporated to yield light yellow oil. This crude product was purified by flash column chromatography.

[0217] IR (cm⁻¹) : 3422 (N-H), 2921 (C-H), 1691 (C=O)

[0218] Mass (Electrospray): 499 (M+1), 497 (M-1)

Example 33: 5-isopropoxycarbonyl-4-(2-ethoxy-6-(8' Z, 11' Z, 14' Z) pentadecatrienyl phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (PPK-29A)

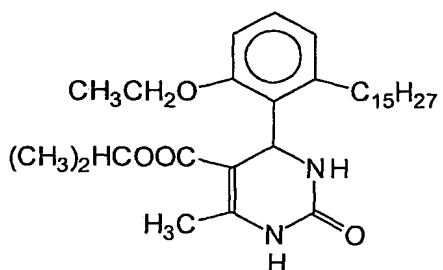


[0219] A solution of isopropylacetoacetate (1.3 g, 8.5 mmol), 2-ethoxy-6-(8' Z, 11' Z, 14' Z) pentadecatrienyl benzaldehyde (3.2 g, 8.5 mmol) and urea (1.1 g, 17 mmol) in tetrahydrofuran (20 mL) was heated to reflux (65-70 °C) in the presence of hydrochloric acid (30%) for 7 h. The reaction mixture after being cooled to room temperature was poured into crushed ice (20 g) and stirred for 5 min. The viscous liquid was extracted with ethylacetate (40 mL) and was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent was evaporated to yield light yellow oil. This crude product was purified by flash column chromatography and recrystallised from hexane to get white crystalline solid of title compound.

[0220] IR (cm⁻¹) : 3421 (N-H), 2920 (C-H), 1690 (C=O)

[0221] Mass (Electrospray): 523 (M+1), 521 (M-1)

Example 34: 5-isopropoxycarbonyl-4-(2-ethoxy-6-(8' Z, 11' Z) pentadecadienyl phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (PPK-29B)



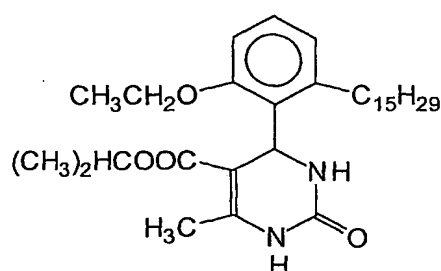
[0222] A solution of isopropylacetoacetate (1.3 g, 8.5 mmol), 2-ethoxy-6-(8' Z, 11' Z) pentadecadienyl benzaldehyde (3.2 g, 8.5 mmol) and urea (1.1 g, 17 mmol) in tetrahydrofuran (20 mL) was heated to reflux (65-70 °C) in the presence of hydrochloric acid (30%) for 7 h. The reaction mixture after being cooled to room temperature was poured into crushed ice (20 g) and stirred for 5 min. The viscous liquid was extracted with ethylacetate (40 mL) and was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium

sulfate, the solvent was evaporated to yield light yellow oil. This crude product was purified by flash column chromatography.

[0223] IR (cm^{-1}) : 3423 (N-H), 2921 (C-H), 1690 (C=O)

[0224] Mass (Electrospray): 525 (M+1), 523 (M-1)

Example 35: 5-isopropoxycarbonyl-4-(2-ethoxy-6-(8' Z) pentadecenyl phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (PPK-29C)

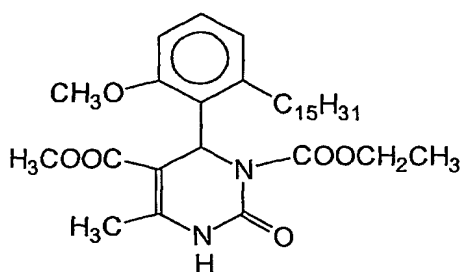


[0225] A solution of isopropylacetoacetate (1.3 g, 8.5 mmol), 2-ethoxy-6-(8' Z) pentadecenyl benzaldehyde (3.2 g, 8.5 mmol) and urea (1.1 g, 17 mmol) in tetrahydrofuran (20 mL) was heated to reflux (65-70 °C) in the presence of hydrochloric acid (30%) for 7 h. The reaction mixture after being cooled to room temperature was poured into crushed ice (20 g) and stirred for 5 min. The viscous liquid was extracted with ethylacetate (40 mL) and was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent was evaporated to yield light yellow oil. This crude product was purified by flash column chromatography.

[0226] IR (cm^{-1}) : 3422 (N-H), 2921 (C-H), 1691 (C=O)

[0227] Mass (Electrospray): 527 (M+1), 525 (M-1)

Example 36: 3,6-dihydro-4-methyl-6-[2-methoxy-6-pentadecylphenyl]-2-oxo-1,5-(2H)-pyrimidinedicarboxylic acid 1-ethyl 5-methyl diester. (PPK-30)



[0228] The solution of 1,4-dihydro-2-[[[4-methoxyphenyl)methyl]oxy]-6-methyl-4-[2-methoxy-6-pentadecylphenyl]-5-pyrimidinecarboxylic acid methyl ester (3 g, 4.6 mmol) in dichloromethane (15 mL) and pyridine (1.5 mL) was treated with ethyl chloroformate (0.6 g, 4.7

mmol) at 0 °C under argon. After the addition was finished reaction was stirred at room temperature for 12 h and then diluted with more dichloromethane. The resultant solution was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent evaporated to yield light yellow oil. This crude product was purified by flash column chromatography and recrystallised from hexane to get white crystalline solid of title compound.

[0229] Melting point : 121-122 °C

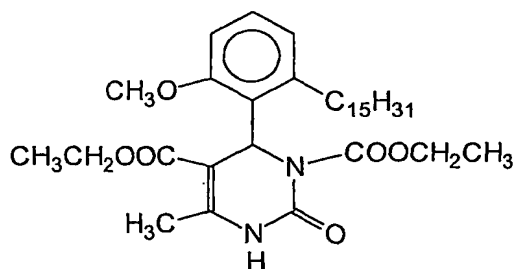
[0230] IR (cm⁻¹) : 3340 (N-H), 2921 (C-H), 1696 (C=O)

[0231] Mass (Electrospray): 559 (M+1), 557 (M-1)

[0232] ¹H NMR (δ ppm) : 8.35 (bs, 1H, D₂O exchangeable, N-H) 7.2 (t, J=8 Hz, 1H, aromatic proton) 6.85 (d, J=8Hz, 1H, aromatic proton) 6.7 (d, J=8Hz, 1H, aromatic proton) 6.55 (s, 1H, C₆-H) 4.25 (q, 2H, J=6 Hz, O-CH₂) 3.75 (s, 3H, O-CH₃) 3.6 (s, 3H, O-CH₃) 3.1 (m, 1H, benzylic) 3.0 (m, 1H, benzylic) 2.25 (s, 3H, allylic) 1.85-1.1 (m, 29H, (CH₂)₁₃ from alkyl chain, CH₃) 0.9 (dt, 3H, terminal CH₃ from alkyl chain).

[0233] bs-broad singlet, t-triplet, d-doublet, s-singlet, m-multiplet, dt-distorted triplet.

Example 37: 3,6-dihydro-4-methyl-6-[2-methoxy-6-pentadecylphenyl]-2-oxo-1,5-(2H)-pyrimidinedicarboxylic acid bis (ethyl ester). (PPK-31)



[0234] The solution of 1,4-dihydro-2-[[[4-methoxyphenyl)methyl]oxy]-6-methyl-4-[2-methoxy-6-pentadecylphenyl]-5-pyrimidinecarboxylic acid ethyl ester (3 g, 4.7 mmol) in dichloromethane (15 mL) and pyridine (1.5 mL) was treated with ethyl chloroformate (0.6 g, 4.7 mmol) at 0 °C under argon. After the addition was finished reaction was stirred at room temperature for 12 h and then diluted with more dichloromethane. The resultant solution was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent evaporated to yield light yellow oil. This crude product was purified by flash column chromatography and recrystallised from hexane to get white crystalline solid of title compound.

[0235] Melting point : 109-110 °C

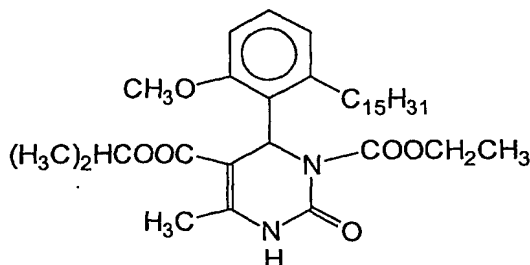
[0236] IR (cm⁻¹) : 3348 (N-H), 2920 (C-H), 1697 (C=O)

[0237] Mass (Electrospray): 573 (M+1), 571 (M-1)

[0238] ¹H NMR (δ ppm) : 8.1 (bs, 1H, D₂O exchangeable, N-H) 7.15 (t, J=8 Hz, 1H, aromatic proton) 6.85 (d, J=8Hz, 1H, aromatic proton) 6.7 (d, J=8Hz, 1H, aromatic proton) 6.55 (s, 1H, C₆-H) 4.1 (m, 4H, O-CH₂) 3.75 (s, 3H, O-CH₃) 3.1 (m, 1H, benzylic) 2.9 (m, 1H, benzylic) 2.25 (s, 3H, allylic) 1.85-1.1 (m, 32H, (CH₂)₁₃ from alkyl chain, CH₃, CH₃) 0.9 (dt, 3H, terminal CH₃ from alkyl chain).

[0239] bs-broad singlet, t-triplet, d-doublet, s-singlet, m-multiplet, dt-distorted triplet.

Example 38: 3,6-dihydro-4-methyl-6-[2-methoxy-6-pentadecylphenyl]-2-oxo-1,5-(2H)-pyrimidinedicarboxylic acid 1-ethyl 5-isopropyl diester. (PPK-32)



[0240] The solution of 1,4-dihydro-2-[[[4-methoxyphenyl)methyl]oxy]-6-methyl-4-[2-methoxy-6-pentadecylphenyl]-5-pyrimidinecarboxylic acid isopropyl ester (3 g, 4.8 mmol) in dichloromethane (15 mL) and pyridine (1.6 mL) was treated with ethyl chloroformate (0.7 g, 4.8 mmol) at 0 °C under argon. After the addition was finished reaction was stirred at room temperature for 12 h and then diluted with more dichloromethane. The resultant solution was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent evaporated to yield light yellow oil. This crude product was purified by flash column chromatography and recrystallised from hexane to get white crystalline solid of title compound.

[0241] Melting point : 100 °C

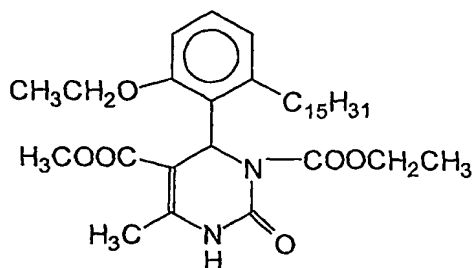
[0242] IR (cm⁻¹) : 3341 (N-H), 2919 (C-H), 1698 (C=O)

[0243] Mass (Electrospray): 587 (M+1), 585 (M-1)

[0244] ¹H NMR (δ ppm) : 8.3 (bs, 1H, D₂O exchangeable, N-H) 7.2 (t, J=8 Hz, 1H, aromatic proton) 6.85 (d, J=8Hz, 1H, aromatic proton) 6.7 (d, J=8Hz, 1H, aromatic proton) 6.57 (s, 1H, C₆-H) 5.0 (m, 1H, OCH(CH₃)₂) 4.25 (q, 2H, J=6 Hz, O-CH₂) 3.75 (s, 3H, O-CH₃) 3.2 (m, 1H, benzylic) 3.0 (m, 1H, benzylic) 2.25 (s, 3H, allylic) 1.9-1.0 (m, 35H, (CH₂)₁₃ from alkyl chain, CH₃, (CH₃)₂) 0.87 (dt, 3H, terminal CH₃ from alkyl chain).

[0245] bs-broad singlet, t-triplet, d-doublet, s-singlet, m-multiplet, dt-distorted triplet.

Example 39: 3,6-dihydro-4-methyl-6-[2-ethoxy-6-pentadecylphenyl]-2-oxo-1,5-(2H)-pyrimidinedicarboxylic acid 1-ethyl 5-methyl diester. (PPK-33)



[0246] The solution of 1,4-dihydro-2-[[[(4-methoxyphenyl)methyl]oxy]-6-methyl-4-[2-ethoxy-6-pentadecylphenyl]-5-pyrimidinecarboxylic acid methyl ester (3 g, 4.7 mmol) in dichloromethane (15 mL) and pyridine (1.5 mL) was treated with ethyl chloroformate (0.7 g, 4.8 mmol) at 0 °C under argon. After the addition was finished reaction was stirred at room temperature for 12 h and then diluted with more dichloromethane. The resultant solution was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent was evaporated to yield light yellow oil. This crude product was purified by flash column chromatography and recrystallised from hexane to get white crystalline solid of title compound.

[0247] Melting point : 103 °C

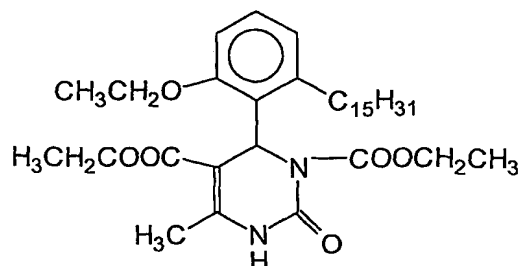
[0248] IR (cm⁻¹) : 3346 (N-H), 2918 (C-H), 1698 (C=O)

[0249] Mass (Electrospray): 573 (M+1), 571 (M-1)

[0250] ¹H NMR (δ ppm) : 7.4 (bs, 1H, N-H) 7.15 (t, J= 7Hz, 1H, aromatic proton) 6.85 (d, J=8Hz, 1H, aromatic proton) 6.7 (d, J=8Hz, 1H, aromatic proton) 6.6 (s, 1H, C₆-H) 4.2 (m, 2H, O-CH₂) 4.0 (q, 2H, J= 6Hz, O-CH₂) 3.6 (s, 3H, O-CH₃) 3.15 (m, 1H, benzylic) 2.95 (m, 1H, benzylic) 2.28 (s, 3H, allylic) 1.85-1.0 (m, 32H, (CH₂)₁₃ from alkyl chain, CH₃, CH₃) 0.9 (dt, 3H, terminal CH₃ from alkyl chain).

[0251] bs-broad singlet, t-triplet, d-doublet, s-singlet, m-multiplet, dt-distorted triplet, q-quartet.

Example 40: 3,6-dihydro-4-methyl-6-[2-ethoxy-6-pentadecylphenyl]-2-oxo-1,5-(2H)-pyrimidinedicarboxylic acid 1,5-diethyl diester. (PPK-34)



[0252] The solution of 1,4-dihydro-2-[[[(4-methoxyphenyl)methyl]oxy]-6-methyl-4-[2-ethoxy-6-pentadecylphenyl]-5-pyrimidinecarboxylic acid ethyl ester (3 g, 4.65 mmol) in dichloromethane (15 mL) and pyridine (1.5 mL) was treated with ethyl chloroformate (0.7 g, 4.7 mmol) at 0 °C under argon. After the addition was finished reaction was stirred at room temperature for 12 h and then diluted with more dichloromethane. The resultant solution was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent was evaporated to yield light yellow oil. This crude product was purified by flash column chromatography and recrystallised from hexane to get white crystalline solid of title compound.

[0253] Melting point : 112 °C

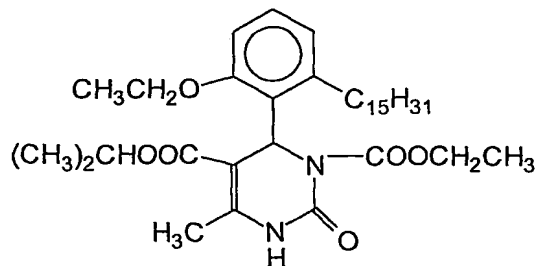
[0254] IR (cm⁻¹) : 3342 (N-H), 2920 (C-H), 1697 (C=O)

[0255] Mass (Electrospray): 587 (M+1), 585 (M-1)

[0256] ¹H NMR (δ ppm) : 7.25 (bs, 1H, N-H) 7.15 (t, J= 7Hz, 1H, aromatic proton) 6.85 (d, J=8Hz, 1H, aromatic proton) 6.7 (d, J=8Hz, 1H, aromatic proton) 6.6 (s, 1H, C₆-H) 4.2 (m, 6H, O-CH₂) 3.2 (m, 1H, benzylic) 2.95 (m, 1H, benzylic) 2.3 (s, 3H, allylic) 1.85-1.15 (m, 32H, (CH₂)₁₃ from alkyl chain, CH₃, CH₃, CH₃) 0.9 (dt, 3H, terminal CH₃ from alkyl chain).

[0257] bs-broad singlet, t-triplet, d-doublet, s-singlet, m-multiplet, dt-distorted triplet, q-quartet.

Example 41: 3,6-dihydro-4-methyl-6-[2-ethoxy-6-pentadecylphenyl]-2-oxo-1,5-(2H)-pyrimidinedicarboxylic acid 1-ethyl 5-isopropyl diester. (PPK-35)



[0258] The solution of 1,4-dihydro-2-[[[(4-methoxyphenyl)methyl]oxy]-6-methyl-4-[2-ethoxy-6-pentadecylphenyl]-5-pyrimidinecarboxylic acid isopropyl ester (3 g, 4.8 mmol) in dichloromethane (15 mL) and pyridine (1.5 mL) was treated with ethyl chloroformate (0.7 g, 4.8 mmol) at 0 °C under argon. After the addition was finished reaction was stirred at room temperature for 12 h and then diluted with more dichloromethane. The resultant solution was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent was evaporated to yield light yellow oil. This crude product was purified by flash column chromatography and recrystallised from hexane to get white crystalline solid of title compound.

[0259] Melting point : 110-111 °C

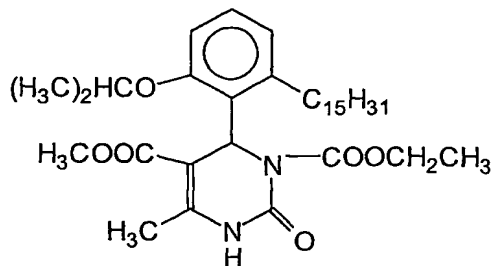
[0260] IR (cm⁻¹) : 3350 (N-H), 2920 (C-H), 1696 (C=O)

[0261] Mass (Electrospray): 601 (M+1), 599 (M-1)

[0262] ¹H NMR (δ ppm) : 7.15 (m, 2H, D2O exchangeable for 1H, N-H, aromatic proton) 6.8 (d, J=8Hz, 1H, aromatic proton) 6.6 (d, J=8Hz, 1H, aromatic proton) 6.5 (s, 1H, C₆-H) 5.0 (m, 1H, OCH(CH₃)₃) 4.25 (m, 2H, CH₂) 4.0 (q, 2H, O-CH₂) 3.25 (m, 1H, benzylic) 3.0 (m, 1H, benzylic) 2.3 (s, 3H, allylic) 1.85-1.0 (m, 38H, (CH₂)₁₃ from alkyl chain, (CH₃)₂, CH₃, CH₃) 0.9 (dt, 3H, terminal CH₃ from alkyl chain).

[0263] bs-broad singlet, t-triplet, d-doublet, s-singlet, m-multiplet, dt-distorted triplet, q-quartet.

Example 42: 3,6-dihydro-4-methyl-6-[2-isopropoxy-6-pentadecylphenyl]-2-oxo-1,5-(2H)-pyrimidinedicarboxylic acid 1-ethyl 5-methyl diester. (PPK-36)



[0264] The solution of 1,4-dihydro-2-[[[(4-methoxyphenyl)methyl]oxy]-6-methyl-4-[2-isopropoxy-6-pentadecylphenyl]-5-pyrimidinecarboxylic acid methyl ester (3 g, 4.7 mmol) in dichloromethane (15 mL) and pyridine (1.5 mL) was treated with ethyl chloroformate (0.7 g, 4.8 mmol) at 0 °C under argon. After the addition was finished reaction was stirred at room temperature for 12 h and then diluted with more dichloromethane. The resultant solution was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent was evaporated to yield light yellow oil. This crude product was purified by flash column chromatography and recrystallised from hexane to get white crystalline solid of title compound.

[0265] Melting point : 120-121 °C

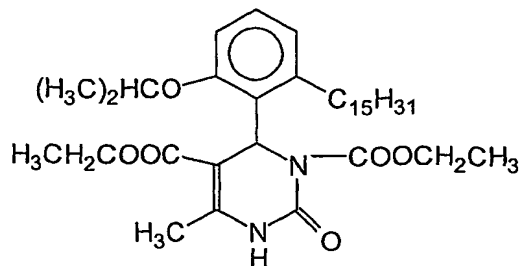
[0266] IR (cm⁻¹) : 3342 (N-H), 2921 (C-H), 1670 (C=O)

[0267] Mass (Electrospray): 587 (M+1), 585 (M-1)

[0268] ¹H NMR (δ ppm) : 7.85 (bs, 1H, N-H) 7.15 (t, J= 7Hz, 1H, aromatic proton) 6.8 (d, J=8Hz, 1H, aromatic proton) 6.7 (d, J=8Hz, 1H, aromatic proton) 6.55 (s, 1H, C₆-H) 4.65 (m, 1H, OCH(CH₃)₂) 4.2 (q, 2H, J= 6Hz, O-CH₂) 3.6 (s, 3H, O-CH₃) 3.0 (m, 2H, benzylic) 2.28 (s, 3H, allylic) 1.95-1.0 (m, 35H, (CH₂)₁₃ from alkyl chain, (CH₃)₂, CH₃) 0.85 (dt, 3H, terminal CH₃ from alkyl chain).

[0269] bs-broad singlet, t-triplet, d-doublet, s-singlet, m-multiplet, dt-distorted triplet, q-quartet.

Example 43: 3,6-dihydro-4-methyl-6-[2-isopropoxy-6-pentadecylphenyl]-2-oxo-1,5-(2H)-pyrimidinedicarboxylic acid 1,5-diethyl diester. (PPK-37)



[0270] The solution of 1,4-dihydro-2-[[[(4-methoxyphenyl)methyl]oxy]-6-methyl-4-[2-ethoxy-6-pentadecylphenyl]-5-pyrimidinecarboxylic acid ethyl ester (3 g, 4.6 mmol) in dichloromethane (15 mL) and pyridine (1.5 mL) was treated with ethyl chloroformate (0.8 g, 4.7 mmol) at 0 °C under argon. After the addition was finished reaction was stirred at room temperature for 12 h and then diluted with more dichloromethane. The resultant solution was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent was evaporated to yield light yellow oil. This crude product was purified by flash column chromatography and recrystallised from hexane to get white crystalline solid of title compound.

[0271] Melting point : 90-92 °C

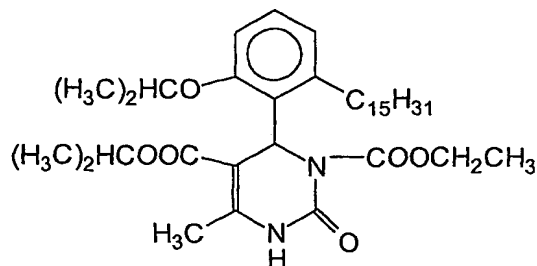
[0272] IR (cm⁻¹) : 3340 (N-H), 2920 (C-H), 1696 (C=O)

[0273] Mass (Electrospray): 601 (M+1), 599 (M-1)

[0274] ¹H NMR (δ ppm) : 7.6 (bs, 1H, N-H) 7.15 (dt, 1H, aromatic proton) 6.8 (d, J=8Hz, 1H, aromatic proton) 6.7 (d, J=8Hz, 1H, aromatic proton) 6.55 (s, 1H, C₆-H) 4.65 (m, 1H, OHC(CH₃)₂) 4.1 (m, 4H, O-CH₂) 3.15 (m, 1H, benzylic) 2.95 (m, 1H, benzylic) 2.2 (s, 3H, allylic) 1.9-1.0 (m, 38H, (CH₂)₁₃ from alkyl chain, CH₃, CH₃, (CH₃)₂) 0.9 (dt, 3H, terminal CH₃ from alkyl chain).

[0275] bs-broad singlet, t-triplet, d-doublet, s-singlet, m-multiplet, dt-distorted triplet, q-quartet.

Example 44: 3,6-dihydro-4-methyl-6-[2-isopropoxy-6-pentadecylphenyl]-2-oxo-1,5-(2H)-pyrimidinedicarboxylic acid 1-ethyl, 5-isopropyl diester. (PPK-38)



[0276] The solution of 1,4-dihydro-2-[[[(4-methoxyphenyl)methyl]oxy]-6-methyl-4-[2-ethoxy-6-pentadecylphenyl]-5-pyrimidinecarboxylic acid isopropyl ester (3 g, 4.5 mmol) in dichloromethane (15 mL) and pyridine (1.5 mL) was treated with ethyl chloroformate (0.85 g, 4.6 mmol) at 0 °C under argon. After the addition was finished reaction was stirred at room temperature for 12 h and then diluted with more dichloromethane. The resultant solution was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent was evaporated to yield light yellow oil. This crude product was purified by flash column chromatography and recrystallised from hexane to get white crystalline solid of title compound.

[0277] Melting point : 88-90 °C

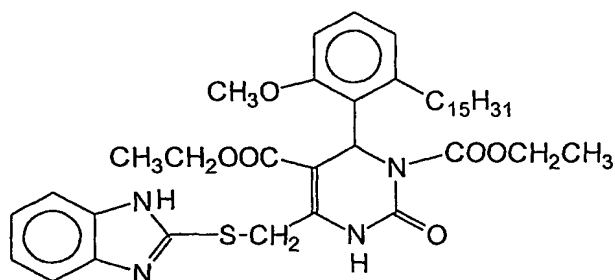
[0278] IR (cm⁻¹) : 3340 (N-H), 2918 (C-H), 1695 (C=O)

[0279] Mass (Electrospray): 615 (M+1), 613 (M-1)

[0280] ¹H NMR (δ ppm) : 7.7 (bs, 1H, N-H) 7.17 (dt, 1H, aromatic proton) 6.8 (d, J=8Hz, 1H, aromatic proton) 6.7 (d, J=8Hz, 1H, aromatic proton) 6.5 (s, 1H, C₆-H) 5.0 (m, 1H, OHC(CH₃)₂) 4.7 (m, 1H, OHC(CH₃)₂) 4.23 (q, J= 6Hz, 2H, O-CH₂) 3.2 (m, 1H, benzylic) 3.0 (m, 1H, benzylic) 2.25 (s, 3H, allylic) 1.9-1.0 (m, 41H, (CH₂)₁₃ from alkyl chain, CH₃, (CH₃)₂, (CH₃)₂) 0.9 (dt, 3H, terminal CH₃ from alkyl chain).

[0281] bs-broad singlet, t-triplet, d-doublet, s-singlet, m-multiplet, dt-distorted triplet, q-quartet.

Example 45: 3,6-dihydro-4-(2'-mercapto-1'H-benzimidazolyl) methyl -6-[2-methoxy-6-pentadecylphenyl]-2-oxo-1,5-(2H)-pyrimidinedicarboxylic acid bis (ethyl ester).



[0282] The solution of 1,4-dihydro-2-[[[(4-methoxyphenyl)methyl]oxy]-6-(2'-mercapto-1'H-benzimidazolyl)methyl-4-[2-methoxy-6-pentadecylphenyl]-5-pyrimidinecarboxylic acid ethyl ester (3 g, 4.9 mmol) in dichloromethane (15 mL) and pyridine (2.0 mL) was treated with ethyl chloroformate (0.7 g, 4.9 mmol) at 0 °C under argon. After the addition was finished reaction was stirred at room temperature for 12 h and then diluted with more dichloromethane. The resultant solution was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent was evaporated to yield light yellow oil. This crude product was purified by flash column chromatography to obtain the title compound.

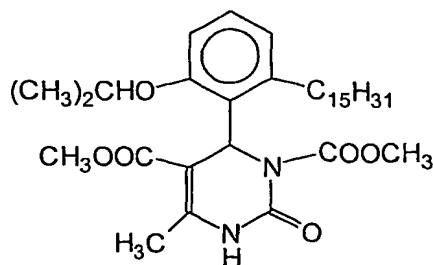
[0283] IR (cm⁻¹) : 3450 (N-H), 2921 (C-H), 1686 (C=O)

[0284] Mass (Electrospray): 721 (M+1), 719 (M-1)

[0285] ¹H NMR (δ ppm) : 8.5 (bs, 1H, D₂O exchangeable, N-H) 7.7 (d, J=6 Hz, 1H, Aromatic proton) 7.5 (m, 1H, Aromatic proton) 7.25 (m, 2H, Aromatic proton) 7.15 (t, J=8 Hz, 1H, Aromatic proton) 6.85 (d, J=8Hz, 2H, Aromatic proton) 5.8 (s, 1H, C₆-H) 4.6 (s, 1H, D₂O exchangeable, N-H) 4.5 (s, 2H, S-CH₂) 4.0 (m, J=6 Hz, 4H, O-CH₂) 3.7 (s, 3H, O-CH₃) 3.1 (m, 1H, benzylic) 2.5 (m, 1H, benzylic) 1.85-1.1 (m, 35H, (CH₂)₁₃ from alkyl chain, CH₃, CH₃, allylic CH₃) 0.9 (dt, 3H, terminal CH₃ from alkyl chain).

[0286] bs-broad singlet, t-triplet, d-doublet, s-singlet, m-multiplet, dt-distorted triplet.

Example 46: 3,6-dihydro-4-methyl-6-[2-isopropoxy-6-pentadecylphenyl]-2-oxo-1,5-(2H)-pyrimidinedicarboxylic acid 1,5-bis (methyl ester).



[0287] The solution of 1,4-dihydro-2-[[[(4-methoxyphenyl)methyl]oxy]-6-methyl-4-[2-isopropoxy-6-pentadecylphenyl]-5-pyrimidinecarboxylic acid methyl ester (3 g, 4.8 mmol) in dichloromethane (15 mL) and pyridine (1.5 mL) was treated with ethyl chloroformate (0.7 g, 4.8 mmol) at 0 °C under argon. After the addition was finished reaction was stirred at room temperature for 12 h and then diluted with more dichloromethane. The resultant solution was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent was evaporated to yield light yellow oil. This crude product was purified by flash column chromatography to obtain the title compound.

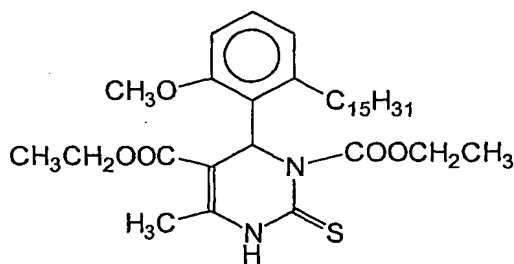
[0288] IR (cm⁻¹) : 3352 (N-H), 2921 (C-H), 1692 (C=O)

[0289] Mass (Electrospray): 573 (M+1), 571 (M-1)

[0290] ¹H NMR (δ ppm) : 8.0 (bs, 1H, D₂O exchangeable, N-H) 7.1 (t, J=8 Hz, 1H, aromatic proton) 6.95 (d, J=8Hz, 1H, aromatic proton) 6.8 (d, J=8Hz, 1H, aromatic proton) 6.65 (s, 1H, C₆-H) 4.0 (s, 3H, COOCH₃) 3.75 (s, 3H, N-COOCH₃) 3.0 (m, 1H, benzylic) 2.85 (m, 1H, benzylic) 2.2 (s, 3H, allylic) 1.85-1.1 (m, 32H, (CH₂)₁₃ from alkyl chain, (CH₃)₂) 0.9 (dt, 3H, terminal CH₃ from alkyl chain).

[0291] bs-broad singlet, t-triplet, d-doublet, s-singlet, m-multiplet, dt-distorted triplet.

Example 47: 3,6-dihydro-4-methyl-6-[2-methoxy-6-pentadecylphenyl]-2-thioxo-1,5-(2H)-pyrimidinedicarboxylic acid bis (ethyl ester).



[0292] The solution of 1,4-dihydro-2-[[[(4-methoxyphenyl)methyl]thio]-6-methyl-4-[2-methoxy-6-pentadecylphenyl]-5-pyrimidinecarboxylic acid ethyl ester (3 g, 4.7 mmol) in dichloromethane (15 mL) and pyridine (1.5 mL) was treated with ethyl chloroformate (0.6 g, 4.7 mmol) at 0 °C under argon. After the addition was finished reaction was stirred at room temperature for 2 h and then diluted with more dichloromethane. The resultant solution was washed with 1N hydrochloric acid, water, sodium bicarbonate and brine. After drying over anhydrous sodium sulfate, the solvent evaporated to yield light yellow oil. This was dissolved in dichloromethane (20 mL) and treated with trifloro acetic acid (2.0 mL) and ethanethiol (1.0 mL). The reaction was stirred at room temperature overnight, and the solvent was evaporated and the crude product was purified by flash column chromatography to obtain the title compound.

[0293] IR (cm⁻¹) : 3350 (N-H), 2921 (C-H), 1696 (C=O)

[0294] Mass (Electrospray): 589 (M+1), 587 (M-1)

[0295] ^1H NMR (δ ppm) : 7.6 (bs, 1H, D_2O exchangeable, N-H) 7.1 (t, $J=8$ Hz, 1H, aromatic proton) 6.8 (d, $J=8$ Hz, 1H, aromatic proton) 6.65 (d, $J=8$ Hz, 1H, aromatic proton) 6.5 (s, 1H, $\text{C}_6\text{-H}$) 4.05 (m, 4H, O- CH_2) 3.7 (s, 3H, O- CH_3) 3.05 (m, 1H, benzylic) 2.95 (m, 1H, benzylic) 2.2 (s, 3H, allylic) 1.85-1.1 (m, 32H, $(\text{CH}_2)_{13}$ from alkyl chain, CH_3 , CH_3) 0.9 (dt, 3H, terminal CH_3 from alkyl chain).

[0296] bs-broad singlet, t-triplet, d-doublet, s-singlet, m-multiplet, dt-distorted triplet

Example 48: Expression of T-type channels in Mammalian Cells.

[0297] T-type calcium channels ($\alpha 1\text{G}$) were stably expressed in HEK293 cells and maintained at 37 °C in DMEM. Cells were released from dishes using trypsin and EGTA or Accutase and studied within 4 hours of isolation. Individual cells were placed on the stage of an inverted microscope and patched with pipettes pulled from aluminasilicate glass capillary tubes, which had resistances of 0.8 -1.5 Mohm. Currents were recorded using an Axopatch 200 (Axon Instruments, Inc.) and pClamp data acquisition software (8.1). The pipette solution contained (in mM): KCl 130, EGTA 11, HEPES 10, MgATP 5, pH = 7.4. The bath solution contained (in mM): NaCl 140, CaCl_2 1, HEPES 10, pH = 7.4. Test compounds were diluted into bath solution to the desired concentration (100 nM -- 10 μM) from a stock solutions (3 or 10 mM in DMSO). Current measurements were made at 20 - 23 °C. Cells were held at -110 mV in order to maximize occupancy in the closed state and depolarized for 100 ms to various potentials. Currents were capacity corrected using 16 - 64 subthreshold responses (voltage steps of 10 or 20 mV) and leak subtracted, based on linear interpolation between the current at the holding potential and 0 mV. Cells were moved from a control chamber to a chamber with test compound and the effect of the drug was assessed using a voltage clamp protocol that stepped to -30 mV for 100 ms from a holding potential of -110 mV once every 5 s. After each 10-13 minutes, the train protocol was interrupted and a full current voltage relationship obtained. In general for each compound, four cells were studied for a minimum of 13 minutes, two in drug at 500 nM and two at 1 μM . In some cases other concentrations were also studied. Data were analyzed using Matlab (Mathworks, Natick, MA). Drug efficacy was estimated using the relationship:

$$\text{Blocked Fraction} = [\text{Drug}] / (\text{IC}_{50} + [\text{Drug}])$$

[0298] The time course of block by drug was fit to a single exponential function:

$$\text{Peak Current} = A * \exp(-t/\tau) + B$$

where A is the initial amplitude of the current, B the final level, t the time after the cell was exposed to drug, and τ , the time constant, i.e. the time it took for the current to be reduced to within 1/e of its final value, B. In general, modification τ s are influenced both by drug on rate and off

rate, although washout was achievable for only one compound, so off rates are so slow (small) that τ can be taken to essentially represent $1/k_{on}$. For some compounds despite the presence of the drug in the chamber, modification occurred with a delay. This was quantified from the time modification was first observed.

Example 49: Block Studies.

[0299] To study block by PPK compounds, cells were held at a sufficiently negative potential that under all ionic conditions studied, channels were fully available (approximately -100mV). Cells were lifted from the chamber bottom and transferred to a second chamber in which solutions with various concentration of drugs were flowing. Reversal of action was achieved by transferring the cell back to the drug-free chamber. Figures show sample current traces obtained during drug wash-in and wash-out (if any) with the time course of the change in peak current displayed below. The cells was depolarized to -30 mV, once every 10 s until current magnitude in drug stabilized. This low frequency of stimulation was chosen to avoid accumulation of channels in an inactivated conformation.

Example 50: Animal Studies.

[0300] Fifteen male spontaneously hypertensive rats (SHR) were used in these studies. The animals were 12 weeks old at arrival and 15 weeks old at the start of study. The animals were divided into five groups, with three animals in each group. The starting, baseline systolic blood pressure for all animals included in the study was 190 – 220 mmHg. The animals were housed in contact bedding. They were fed Purina 5008. Six days after arrival, the animals were trained in the blood pressure apparatus for four days before the start of the study.

[0301] Compounds were administered to the animals by tail vein injection. Dose levels were 0.5 mL. In each study, one group of animals served as control, while the others were injected with a dosage of a compound.

[0302] The study was conducted using the schedule set forth below:

Day	Procedure
-13	Animals arrive
-7 to -3	Train Animals in BP apparatus
1	1. Take baseline BP reading on all groups 2. Dose animals 3. Take BP readings at 5 and 10 hr following injection
2	1. Take 24 hr BP reading on all animals 2. Dose animals 3. Take BP reading at 36 hr following initial dose
3	1. Take 48 hr BP reading on all animals 2. Dose animals 3. Take BP reading at 60 hr following initial dose
4	1. Take 72 hr BP reading on all animals

[0303] References:

Methods of testing for pharmacological activities of the compounds:

1. Against calcium T-type channels (low voltage activated calcium channels):
 - a) L. Lacinova, N. Klugbauer, F. Hofmann "Regulation of the calcium channel α_{1G} subunit by divalent cations and organic blockers" *Neuropharmacology*, 39, 1254-1266 (2000).
 - b) J. P. Clozel, E. A. Ertel, S.I. Ertel "Discovery and main pharmacological properties of mibefradil (Ro 40-5967), the first selective T-type calcium channel blocker" *Journal of hypertension* 15, S17-S25 (1997).
 - c) G. Mehrke, X. G. Zong, V. Flockerzi, F. Hofmann "The Ca^{2+} channel blocker Ro 40-5967 blocks differently T-type and L-type Ca^{2+} channels" *Journal of Pharmacology and Experimental Therapeutics*, 271, 1483-1488 (1994).
 - d) S. Richard, S. Diochot, J. Nargeot, M. Baldy-Moulinier, J. Valmier "Inhibition of T-type calcium currents by dihydropyridines in mouse embryonic dorsal root ganglion neurons" *Neuroscience Letters* 132, 229-234 (1991).
 - e) R. S. I. Chaung, H. Jaffe, L. Cribbs, E. Perez-Reyes, K. J. Swartz "Inhibition of T-type voltage gated calcium channel by a new scorpion toxin" *Nature Neuroscience*, 1, 668-674 (1998).
2. Against calcium L-type channels (high voltage activated calcium channels):
 - a) B. Z. Peterson, C. D. DeMaria, D. T. Yue "Calmodulin is the Ca^{2+} sensor for Ca^{2+} -dependent inactivation of L-type calcium channels" *Neuron*, 22, 549-558 (1999).
 - b) G. C. Rovnyak, S. D. Kimball, B. Beyer, G. Cucinotta, J. D. DiMarco, J. Gougoutas, A. Hedberg, M. Malley, J. P. McCarthy, R. Zhang, S. Moreland "Calcium Entry Blockers and Activators: Conformational and Structural Determinants of Dihydropyrimidine Calcium Channel Modulators" *Journal of Medicinal Chemistry*, 38, 199-129 (1995).
3. Against N-, P/Q-, and R- types of calcium channels:
 - a) Stea, A.; Soong, T. W.; Snutch, T. P. "Voltage gated calcium channels," in *Handbook of Receptors and Channels; Ligand- and Voltage-Gated Ion Channels* (North RA ed.), 1995, 113-152, CRC Press Inc., Boca Raton, Florida.
 - b) Zamponi, G. W. "Antagonist sites of voltage dependent calcium channels," *Drug Development Research*, 1997, 42, 131-143.
 - c) Neelands, T. R.; King, A. P.; Macdonald, R. L. "Functional expression of L-, N-, P/Q-, and R-type calcium channels in the human NT2-N cell line," *J. Neurophysiol.* 2000, 84(6), 393-401.

CONCLUSION

[0304] Thus, those of skill in the art will appreciate that the compounds and uses disclosed herein can be used as calcium channel blockers, providing a therapeutic effect.

[0305] One skilled in the art will appreciate that these methods and compounds are and may be adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The methods, procedures, and compounds described herein are presently representative of preferred embodiments and are exemplary and are not intended as limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art which are encompassed within the spirit of the invention and are defined by the scope of the claims.

[0306] It will be apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention.

[0307] Those skilled in the art recognize that the aspects and embodiments of the invention set forth herein may be practiced separate from each other or in conjunction with each other. Therefore, combinations of separate embodiments are within the scope of the invention as claimed herein.

[0308] All patents and publications mentioned in the specification are indicative of the levels of those skilled in the art to which the invention pertains.

[0309] The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of" and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions indicates the exclusion of equivalents of the features shown and described or portions thereof. It is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

[0310] In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group. For example, if X is described as selected from the group consisting of bromine, chlorine, and iodine, claims for X being bromine and claims for X being bromine and chlorine are fully described.

[0311] Other embodiments are within the following claims.